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PROGRESSIVE PARALYSIS OF THE NERVUS INTEROSSEUS DORSALIS: PATHOLOGICAL FINDINGS IN ONE CASE

FRANK J. OTENASEK,

From the Department of Surgery (Neurosurgery) of the Johns Hopkins University School of Medicine

Isolated cases of paralysis of the deep motor branch of the radial nerve (n. interosseus dorsalis) must not be very uncommon, although but few cases are recorded in the literature. Most of these have been of acute traumatic origin. Koch (1) reports such a case of section of the nerve in the supinator muscle by a stab wound, Mowell (2) after an injury by a circular saw. Occasionally a gunshot wound will, by coincidence, sever the motor and spare the sensory branches as in the cases of Marie, Meige, and Patrikios (3), and of Roussy and Branche (4). Grigoresco and Iordanesco (5) recorded a case believed to have come on after pressure on the nerve during sleep, following a sprain.

Occasionally instances of paralysis of the n. interosseus dorsalis appear to be progressive, unassociated with acute trauma and with no obvious gross lesion to account for the symptoms. An interesting account of a case possibly caused by chronic trauma was given by Guillain and Courtellement (6). Their patient, an orchestra conductor, developed weakness of extension of his fifth right finger. Ten days later extension of the fourth finger was also impaired. In six months the third finger was involved. No sensory changes appeared. Some tenderness could be elicited at the point of entrance of the n. interosseus dorsalis into the supinator muscle. It was discovered that the patient held his baton with the fourth and fifth fingers. Guillain and Courtellement ascribed the paralysis to the repeated movements of pronation and supination made while directing the orchestra.

There have been reported a few cases of isolated paralysis of the nervus interosseus dorsalis in which there was not even a history of such chronic trauma as the possible etiologic agent. Woltman and Learmonth (7) reviewed the literature on the subject and reported five cases, in one of which exploration of the nerve was carried out.

"When the supinator brevis was exposed it was found that instead of passing through the supinator the nerve passed superficially between the muscle and the aponeurosis of the common extensor. The nerve had molded a groove across the fibers of the supinator, and it seemed possible that repeated mechanical trauma imposed on the nerve by the

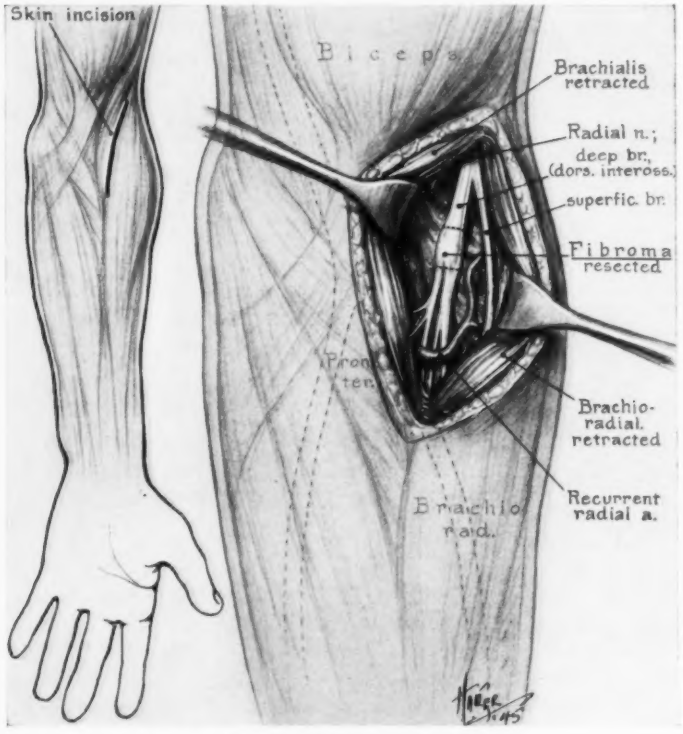

FIG. 1. OPERATIVE EXPOSURE OF TUMOR

contractions of the supinator brevis might have given rise to the neuritis." The normal course of the nervus interosseus dorsalis is through the substance of the supinator muscle.

REPORT OF A CASE

W. C., a white male of 21 years, complained of weakness of the left hand. At the age of 13, without history of injury of any kind, he first noted weakness of

dorsiflexion of the left thumb. This gradually worsened over a period of several years, until all fingers except the fifth were involved. He then developed weakness of extension of the wrist and finally a typical wrist drop. Examination showed extensor paralysis of the left hand and wrist, the fifth finger being partially spared.

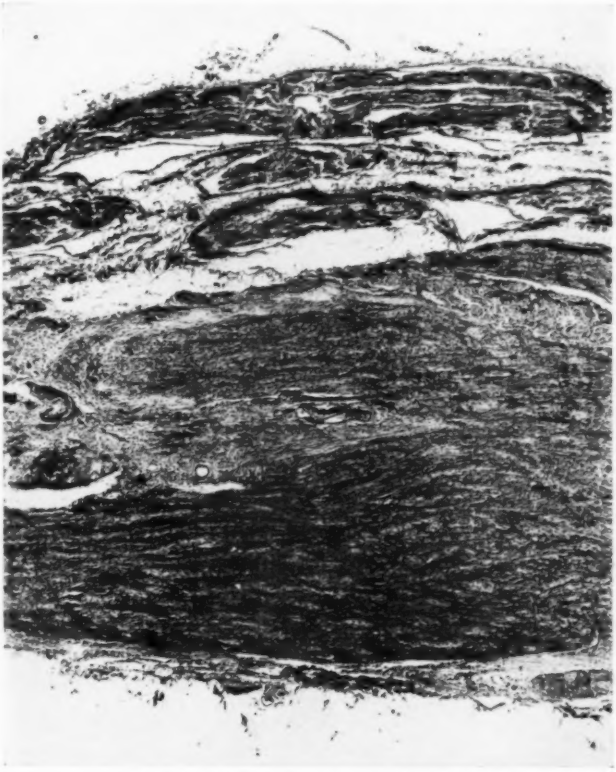

FIG. 2. HEMATOXYLIN AND EOSIN ×30

There was some weakness of supination. Marked atrophy of all the extensor muscles was present. No subjective or objective sensory changes were made out. No lesion could be seen or palpated over the course of the radial nerve or its deep branch. The diagnosis of a progressive lesion of the deep motor branch in the region of the supinator muscle was made by Dr. Frank Ford, who referred the patient to me.

Exploration of the nerve was carried out on April 28, 1945, exposure being made along the ulnar aspect of the brachioradialis muscle (Fig. 1). The main trunk of

the radial nerve was followed distally until the superficial (sensory) branch could be distinguished from the deep motor branch. Just below the division, on the motor branch, could be seen and felt a tiny nodule on the nerve, not more than 2 mm. in diameter. It was taken to be a neuroma. There was nothing in the

FIG 3. HEMATOXYLIN AND EOSIN ×300

external appearance of the nerve or its sheath to suggest the possibility of a previous trauma. The tumor was resected and the nerve sutured in continuity.

Microscopical study was made by Dr. Sam Blackman, whose notes are as follows: "Microscopically, along one margin of the specimen, there is a longitudinal section of a normal branch of the nerve (Fig. 2). The trichrome stains show the myelin sheaths and the axis cylinders. The larger branch of the nerve, however, is largely composed of connective tissue which is very cellular, but also contains many collagen fibers (Fig. 3). In the trichrome stain it is difficult to find

axis cylinders or myelin sheaths. This lesion differs from a neuroma in that it consists chiefly of a new growth of connective tissue. It might be considered either a scarred nerve or a fibrous tumor of the nerve. There is no history of trauma, and the absence of inflammation together with the history is some evidence against the lesion being a scar. It seems probable that it is a fibroma, although it is not at all a typical plexiform fibroma."

At the time of writing (two years after operation) there is no sign of return of function.

COMMENT

The history and physical findings in this case correspond very accurately to those in the five cases reported by Woltman and Learmonth (7), except that in the latter the weakness usually involved the fifth finger first, whereas in the present case, the thumb was affected first. In every case the extensor paralysis was progressive, there was marked atrophy and there were no subjective or objective sensory changes. The lesion had to be limited to the n. interosseus dorsalis. The unique anatomical course of the nerve through the supinator muscle has led to the assumption that some mechanical factor involved in this muscle-nerve relationship has resulted in the loss of function of the nerve. The present case illustrates the occurence of an etiologic factor which is neoplastic and bears only an incidental relationship to the supinator muscle. It suggests that early diagnosis and surgical exploration of the nerve may lead to restoration of function.

BIBLIOGRAPHY

1. Koch, S. L.: Injuries of the radial nerve. Quart. Bull. Northwestern Univ. M. School, **17**, 1, 1943.
2. Mowell, J. W.: Posterior interosseus nerve injury. Internat. Clin., **2**, 188, 1921.
3. Marie, P., Meige, H., and Patrikios: Paralysie radiale dissociée simulant une griffe cubitale. Rev. Neurol., **31**, 132, 1917.
4. Roussy, G., and Branche, J.: Deux cas de paralysies dissociées de la branche postériéure du radial, à type de pseudo-griffe cubitale. Rev. Neurol., **32**, 312, 1917.
5. Grigoresco, D., and Iordanesco, G.: Un cas rare de paralysie partielle du nerf radial. Rev. Neurol., **56**, 102, 1931.
6. Guillain, G., and Courtellement: L'action du muscle court supinateur dans la paralysie du nerf radial. Pathogénie d'une paralysie radiale incomplète chez un chef d'orchestre. Presse Méd., **1**, 50, 1905.
7. Woltman, H. W., and Learmonth, J. R.: Progressive paralysis of the nervus interosseus dorsalis. Brain, **57**, 25, 1934.

THE MECHANISM OF EXCRETION OF AMMONIUM THIOSULFATE*

JOHN FRANKLIN†, JACQUES GENEST AND ELLIOT NEWMAN

With Technical Assistance of MARGOT ROBINSON and MARION BIRMINGHAM

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Thiosulfate has been extensively employed in the treatment of heavy metal and cyanide poisonings and is reported to have therapeutic value in certain vascular diseases. This background of frequent clinical use has revealed that the drug possesses no serious toxic actions. It is an old observation that thiosulfate is readily excreted by the kidney and its use as a measure of renal function was suggested by Nyiri in 1923 (1).

Gilman and associates (2) in the course of studies on the antidotal value of thiosulfate against chemical warfare agents, found in dogs that the renal clearance of thiosulfate was identical to the creatinine clearance or the glomerular filtration rate. In other words, the thiosulfate ion is excreted only by the glomerulus, a fact which labels it as the only inorganic ion which is known to be excreted independently of tubular function.

Newman, Gilman and Philips (3) extended the studies on thiosulfate clearance to the human kidney and concluded that thiosulfate and inulin clearances are identical. The criteria for establishing sodium thiosulfate as a measure of glomerular filtration rate have therefore been fulfilled.

Because of the unique mechanism of excretion of this electrolyte it could be expected that the excretion of thiosulfate at the rate of glomerular filtration would obligate an equal rate of excretion of base. Preliminary studies in patients of the partition of urinary base excreted with the thiosulfate anion revealed that the total thiosulfate excretion was covered mainly with sodium except in a few individuals with diseased kidneys.

* Supported by a grant from the Life Insurance Medical Research Fund and from the G. D. Searle Co.

† Clinical Fellow, American College of Physicians 1946–47.

The present study was undertaken to determine the effectiveness of thiosulfate in removing extracellular sodium in the dog, as well as its effect on the pattern of excretion of other electrolytes. For this purpose the ammonium salt was used to present the kidney with the thiosulfate anion without added sodium in order to obligate the removal of intrinsic extracellular sodium.

METHODS

Four types of experiments were performed on adult female dogs weighing from 13 to 20 kilograms kept on a constant weighed diet with water ad lib.

1. A short experiment in which ammonium thiosulfate[1] was administered intravenously for one hour and the pattern of urinary electrolyte excretion studied during the infusion and post infusion periods.
2. An exhaustive experiment in which ammonium thiosulfate was administered continuously intravenously until exitus of the dog, the urine and serum being analyzed at frequent intervals for changes in the partition of electrolytes.
3. A single dose oral experiment in which the urine was studied for a follow up period of seven hours.
4. A chronic experiment in which the drug was administered orally to two dogs for a period of three and a half days and the urine studied for an interval sufficiently long to provide pre- and post-experimental controls.

The dogs were kept in metabolic cages, and daily records were maintained of the dog's weight, temperature, food and water intake and urinary output.

Urine collections in short experiments were made by catheter and the bladder washed with sterile water to insure complete collection. Twenty four hour collections were completed by catheterization every morning. Acetic acid and thymol were used as preservatives in the 24 hour urine collection bottles.

A commercially prepared diet was fed which upon chemical analysis was found to provide the following:

Total N	4.0 gms./100 gms. diet
Sodium	12.3 meq./100 gms. diet

[1] Supplied by Winthrop Chemical Company; Mr. J. R. Lucas, Baltimore.

Potassium	11.7 meq./100 gms. diet
Phosphate	78.0 meq./100 gms. diet
Chlorides	11.7 meq./100 gms. diet

In addition the diet provided adequate amounts of carbohydrate, fat and other essential minerals. The animals gained weight during control periods and never revealed evidences of a dietary deficiency.

The chemical analyses of urine and serum involved minor modifications of accepted quantitative techniques.

Sodium and potassium determinations on both urine and serum were made by the flame photometer (4). This method was adequately tested by Hald and Peters (5) and compared with standard quantitative chemical techniques. Our equipment has been similarly checked and sufficient duplicate determinations have been made to assure us that readings are reproducible (6).

The Harvey (7) modification of the standard Volhard (8) titration method for chlorides was further modified because addition of nitric acid to urine containing thiosulfate caused precipitation of colloidal sulfur and organic matter, which made the end point difficult to read. The addition of enough nitric acid to precipitate the thiosulfate, followed by thorough clearing with permanganate, before the addition of the standard nitric acid-silver nitrate solution, eliminated the interfering color.

Similarly the standard Folin (9) method for the quantitative determination of total sulfate (ethereal plus inorganic sulfate) was modified because of the presence of thiosulfate. The latter was precipitated from the urine as colloidal sulfur by the addition of nitric acid and heating. The sulfur was then removed by addition of infusorial earth and filtering. An aliquot of the filtrate was used for sulfate determination.

Phosphates were determined by the method of Fiske and Subbarrow (10), and thiosulfate in urine and serum by the method of Newman, Gilman and Philips (3). The Albanese (11) method and apparatus were employed in ammonium determinations. Total proteins were determined by the Macro Kjeldahl technique, and NPN by the Buell (12a) modification of the Kock, McMeekin (12) method. Gentzkow's (13) method for urea nitrogen was employed. CO_2 combining power was determined by the volumetric method of Van Slyke (14).

The amount of ammonium thiosulfate employed is given in the dis-

cussion of the separate experiments. When given orally it was powdered and put in gelatin capsules.

RESULTS

The effect of short intravenous administration of ammonium thiosulfate is illustrated in Figure 1. To a dog weighing 17.35 kilograms on 500 grams of diet, 2.7 grams of ammonium thiosulfate were administered in an isotonic infusion during the first hour and urine collections were made at hourly intervals for a total of four hours. The last column in Figure 1 represents the hourly rate of excretion of electrolytes during the remainder of the 24 hour period.

The total urine volume for this day was 1190 cc.; an increase of 400 cc. over the average daily output. The hourly urine volume follows closely the pattern of total sodium excretion.

There is a slight increase in ammonia excretion which may be due to stimulation by the acid ion of the base-saving ammonia-producing mechanism of the kidney.

The increase in sodium excretion is most striking. 40 Meq. of sodium appeared during the four hour experimental period whereas the total excretion for the day was only 47 Meq. The 7 Meq. excreted during the post experiment period indicates that a compensatory retention of sodium occurred following the large initial loss. The total excretion of sodium for the day was not greatly increased above the average because of the short duration of the experiment, but $\frac{4}{7}$ of this daily total was excreted in four hours.

There is a slight but delayed increase in potassium excretion.

Thiosulfate occupies the largest portion of the anion block and represents a total excretion of 31 Meq. or a total recovery of 81% of the administered drug. The SO_4 excretion is increased above the average daily excretion sufficiently to account for that portion of thiosulfate not recovered. If one adds the portion of SO_4 which represents oxidized thiosulfate to the thiosulfate block, the block representing sodium excretion is practically superimposable or equal.

Chloride and phosphate ions were excreted in negligible amounts during the experimental period, appearing after the kidney had cleared the thiosulfate. The total 24 hour excretion of chloride on the day of experiment was decreased.

The pattern of electrolyte response to ammonium thiosulfate in both

urine and serum when the drug was administered intravenously until exitus of the animal is shown in Figure 2.

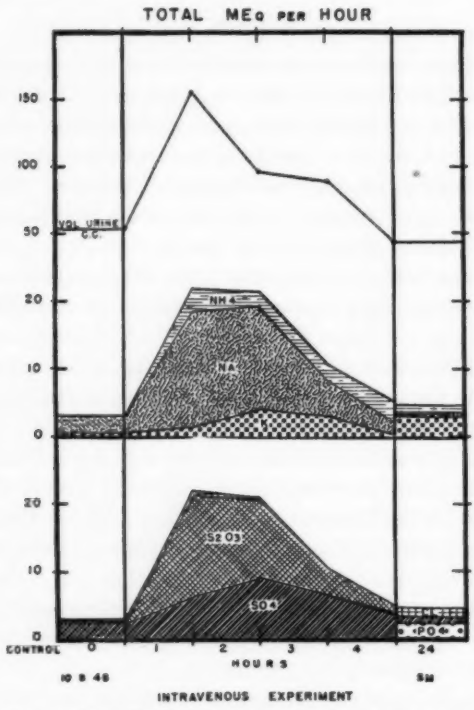

FIG. 1. THE EFFECT OF INTRAVENOUS ADMINISTRATION

Dog SM. Fasting, Unanesthetized, Wt. 17.35 kilograms. Diet 500 grams daily. 2.7 grams ammonium thiosulfate intravenously as isotonic infusion during first hour. Urine collections hourly for four hours. Control hour and hourly rate of excretion of remaining 24 hours shown. Ordinate is total milliequivalents.

A total of approximately 25 gm. of ammonium thiosulfate was given by constant infusion to a dog weighing 17 kilograms until death occurred in six hours.

The changes in serum are represented as increments above or below a base line of control values.

The pattern of electrolyte response in the urine is similar to the short intravenous experiment, with a striking increase in sodium excretion

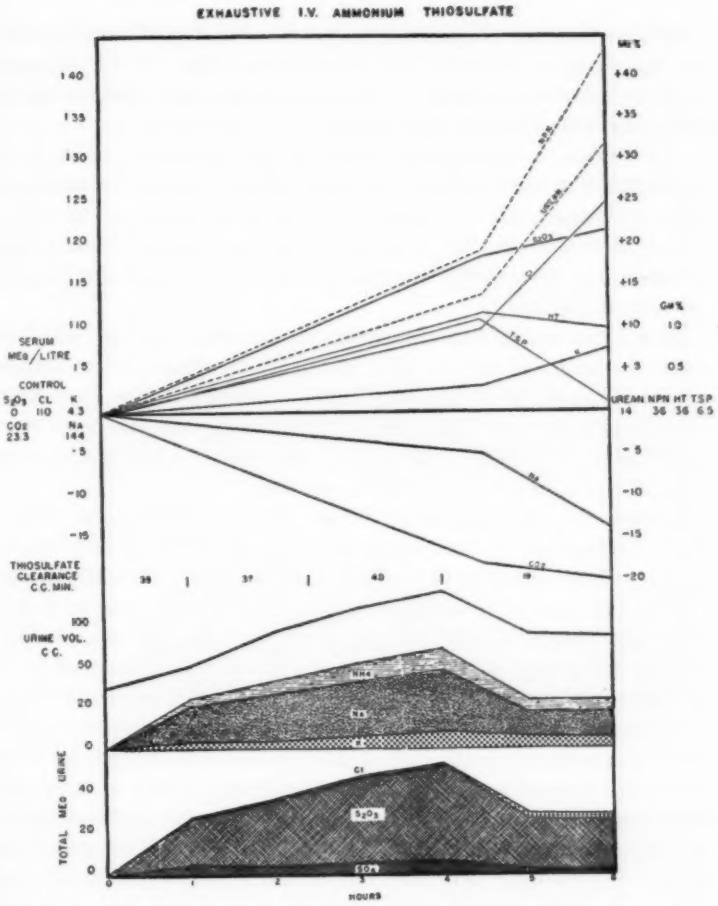

FIG. 2. THE EFFECT OF CONTINUOUS INTRAVENOUS ADMINISTRATION

Dog P, Fasting, Anesthetized with Nembutal, Wt. 17.0 kilograms. 25 grams ammonium thiosulfate intravenously in 700 cc. of water given at a constant rate during six hours until exitus. Shows urine volume, changes in serum concentrations as increments above or below normal values, and hourly total excretion of electrolytes calculated in milliequivalents. Thiosulfate clearance in cc/min. T. S. P. is total serum protein; Ht is hematocrit.

representing a total of 115 milliequivalents in six hours and a delayed but definite increase in potassium excretion.

On the anion side, thiosulfate occupies the major portion of the block and represents a total of 13 gm. of recovered drug. SO_4 is increased as in the short experiment. Chloride excretion was minimal and no phosphate was recovered in the urine.

The decreased urine volume during the last collection period can be correlated with other evidence of renal failure; first, a decreased glomerular filtration rate as measured by thiosulfate clearance and second, a rising NPN and urea N. The concentrations of urea and non protein nitrogen rose, particularly terminally, to levels of 57 and 64 milligrams per cent, respectively.

Most important in this experiment are the serum changes which indicate the probable mechanism of death. The serum sodium concentration fell from 144 to 125 and the serum potassium rose from 4.4 to 12 milliequivalents per liter. With these striking changes there was a rise of serum chloride of 25 Meq. and a fall of the CO_2 combining power from 23.3 to a final level of 4 Meq. per liter.

Evidence of hemoconcentration and loss of extracellular fluid is shown by the rise in the hematocrit and the total serum protein concentration. One might at first conclude that the loss of extracellular fluid causing the signs of hemoconcentration was due to a marked loss of water with the thiosulfate diuresis. Actually there was no overall loss of body water in this experiment since the water administered in the infusion of thiosulfate approximately equalled the urine output.

If the contraction of extracellular volume was not due to negative fluid balance, an alternative explanation is that the marked loss of sodium with lowered sodium concentration caused a shift of water into muscle cells. Analysis of the water content of this dog's muscle by Dr. Kenneth Zierler showed an increase to 89% water, normal being 76%.[2] Concomitant with the shift of water from extracellular fluid into cells it is likely that cell potassium escaped, thus accounting for the marked increase in serum potassium to a level which is usually lethal. The phenomenon of shift of extracellular water into cells with a release of potassium in the other direction due to marked loss of sodium has been the subject of much recent experimental and clinical study by Darrow, Finch and others (15, 16).

[2] Determined by difference between whole wet weight and dry weight.

At autopsy, no gross or microscopic pathology was seen in the heart, kidneys or adrenal glands of this dog.[3]

In Figure 3 is illustrated the pattern of electrolyte excretion in response to 5 gm. of ammonium thiosulfate administered orally to a dog

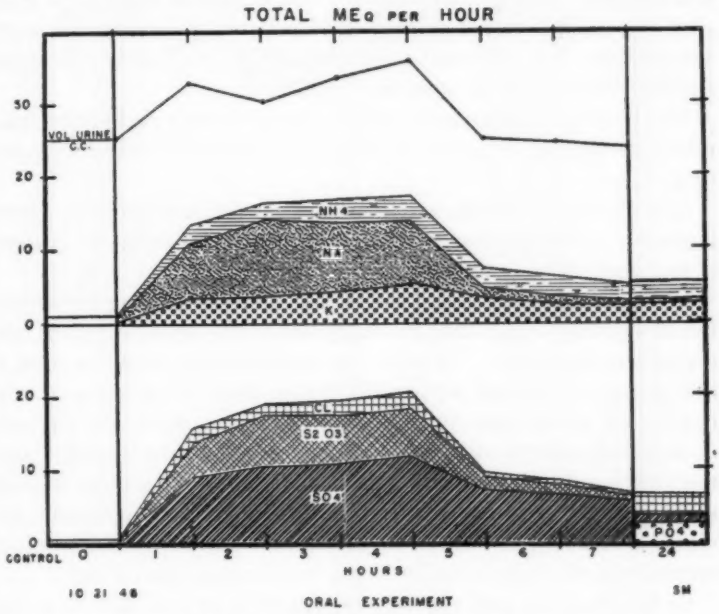

FIG. 3. THE EFFECT OF A SINGLE ORAL DOSE

Dog SM, Fasting, Unanesthetized, Wt. 17.75 kilograms, diet 500 grams daily. 5 grams ammonium thiosulfate in 20 cc. of water by duodenal tube. Control hour total electrolyte excretion shown and hourly total electrolyte excretion in milliequivalents for seven hours following administration. Hourly rate of excretion for remaining 17 hours shown. Hourly urine volume in cc.

weighing 17.75 kilograms on 500 grams of diet daily. The urine was collected at hourly intervals for seven hours.

The pattern of response is similar to that illustrated in Fig. 1 with an increase in ammonia, and a dramatic increase in sodium excretion,

[3] Sections examined by Dr. Mitchell Miller, Instructor in Pathology.

followed by a post experiment period of sodium retention. There is a delayed increase in potassium excretion.

The rate of thiosulfate excretion is slower than in the intravenous experiment. The total recovered was 32 Meq. or 48% of the amount administered. The greatly increased SO_4, a total of 84 Meq., is sufficient to account for that portion of thiosulfate not recovered as such, and indicates that after oral administration approximately half of the administered thiosulfate is oxidized to SO_4.

No phosphate was excreted during the experiment period and chloride excretion was not as low as after intravenous administration of the drug.

Again the sodium block, and thiosulfate plus sulfate blocks are superimposable. The increase in urine volume follows closely the pattern of increased sodium excretion.

In Figure 4 is summarized the control data on one dog for twenty five days during which time two intravenous experiments and one oral experiment were done. On day 1 five grams and on day 8 two and a half grams of ammonium thiosulfate were given intravenously. On day 21, five grams were given orally. The general pattern of response on experiment days consists of increased urine flow; low chloride excretion; increased sulfate excretion particularly after oral administration; slight increase in ammonia excretion; little significant potassium increase; and finally an increase in sodium excretion followed by sodium retention particularly after the larger intravenous dose on day 1.

On the whole the total electrolytes excreted in 24 hour periods do not show marked increases except for sulfate because the duration of the administration was only for a fraction of the day, so that compensatory retention for the remainder of the day largely balanced the early loss.

Other variations in urine volume and electrolyte excretion are the usually spontaneous variations of a dog on a constant diet with water ad lib.

The effects of chronic oral administration of ammonium thiosulfate were studied in two dogs and results are illustrated in Figures 5 and 6. Each received a total of 35 grams of the drug over a period of three and a half days.

The total recoveries of thiosulfate in urine in these experiments were 85 and 93 per cent in Figures 5 and 6 respectively. Of the total re-

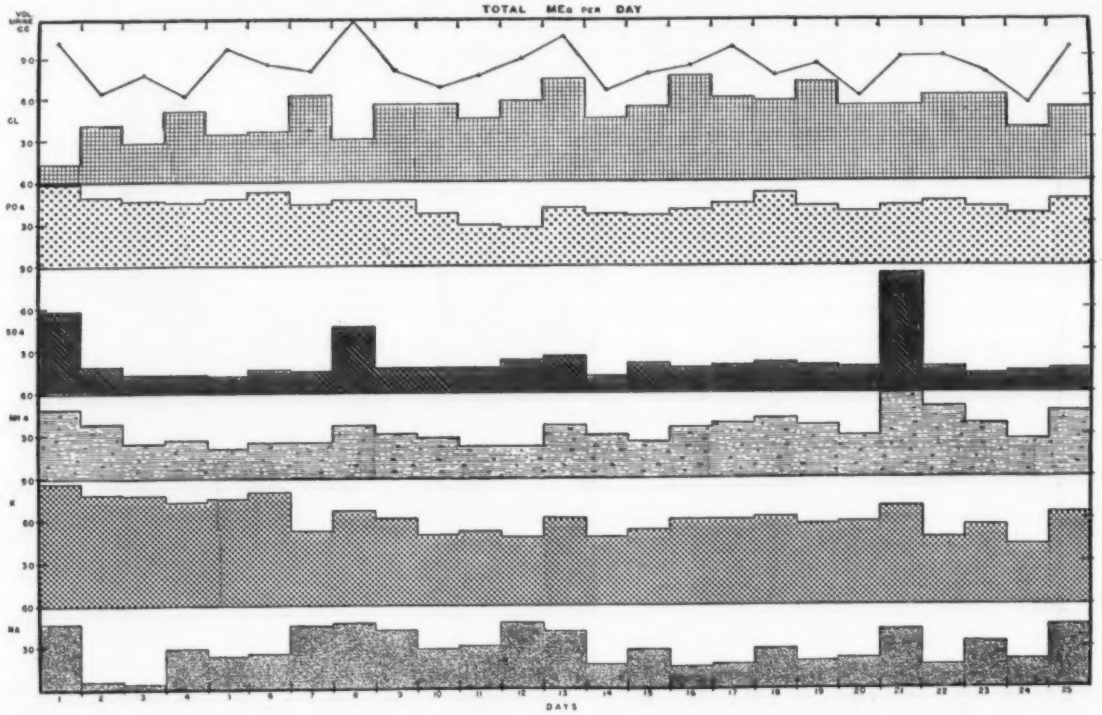

FIG. 4. Illustrating routine control 24 hour determinations of total electrolytes in milliequivalents and the effect on sulfate excretion of intravenous ammonium thiosulfate on days 1 and 8 and oral ammonium thiosulfate on day 21. Dog SM, Wt. 18 kilograms, Diet 500 grams daily.

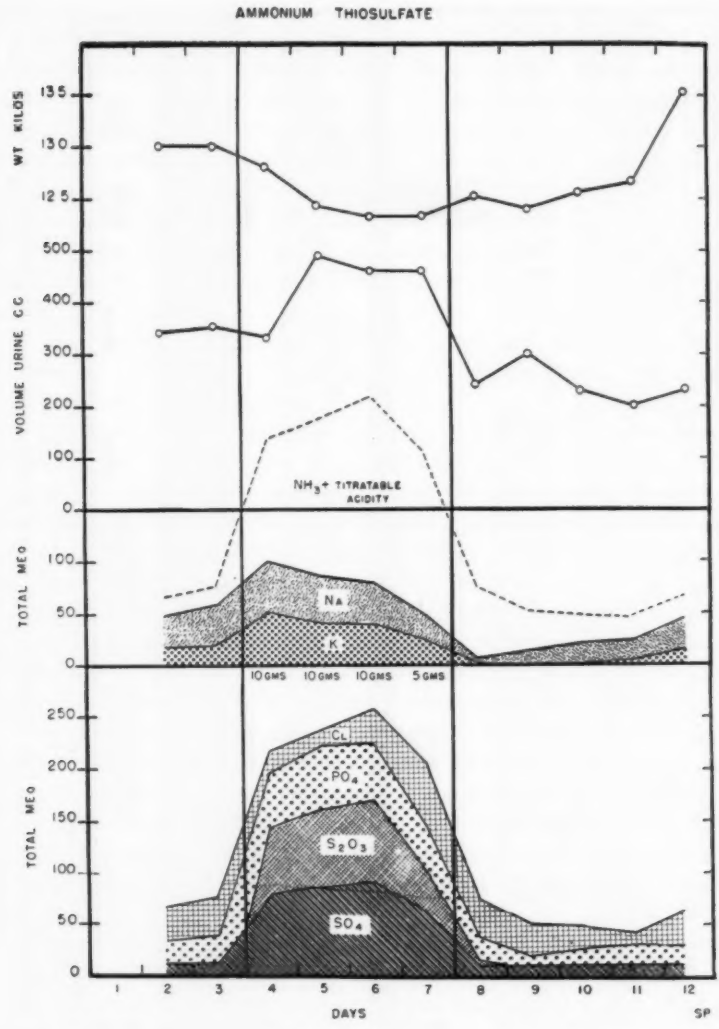

FIG. 5. Oral administration of 35 grams of ammonium thiosulfate in four days. Two days control and four days following administration recorded. Dog SP, Wt. 13.0 kilograms, Diet 300 grams daily.

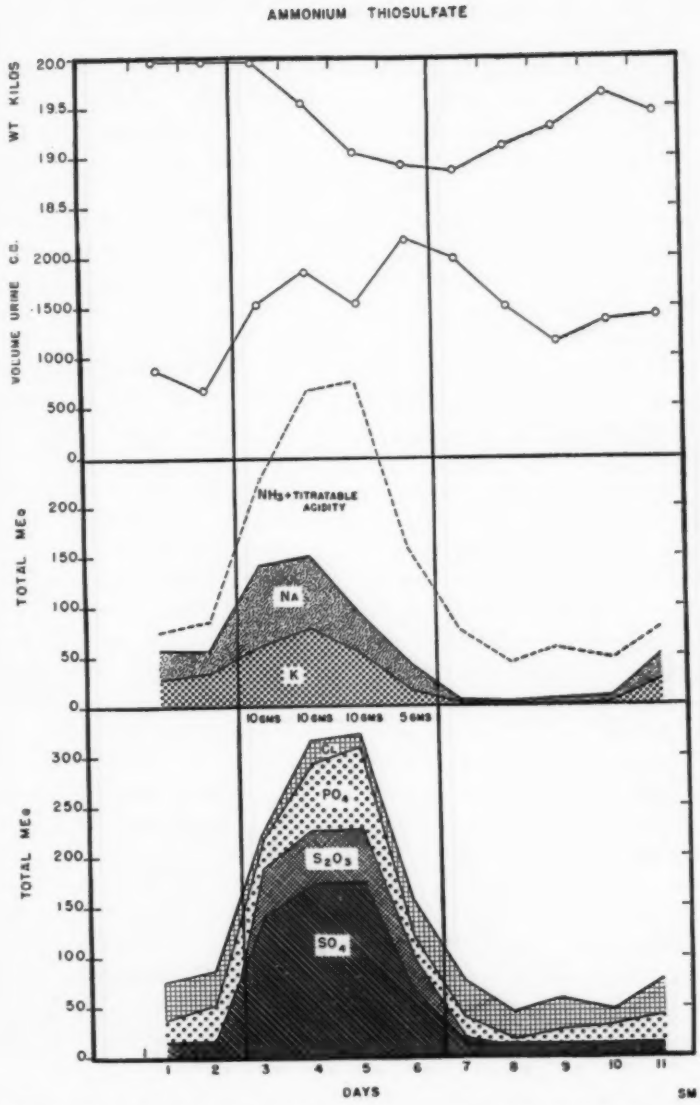

FIG. 6. Oral administration of 35 grams of ammonium thiosulfate in four days. Two days control and four days following administration recorded. Dog SM. Wt. 20 kilograms, Diet 250 grams daily.

covered 44 to 66 per cent was present as the thiosulfate ion in the urine and the balance as the sulfate ion. As thiosulfate yields two sulfate ions upon oxidation, the larger sulfate excretion is thus explained.

The pattern of sodium and potassium excretion is similar to but less dramatic than in the previously described experiments. The dog in Figure 6 doubled her average daily sodium excretion during the period of drug administration, excreting a total of 107 Meq. of sodium in excess of an amount calculated from the preceding control period. The total potassium lost during the experiment almost equaled the sodium loss, being 92 Meq. in excess of the control excretion.

The dog in Figure 5 excreted less sodium with the same amount of the drug, her total excess being only 30 Meq., but potassium excretion was significantly increased over the control excretion to 80 Meq.

The difference in sodium loss in the two dogs is not accounted for on the basis of dose-body weight relationship since dog No. 1 which lost more sodium was heavier and received an equal amount of the drug. The amount of the post-administration retention of sodium was roughly proportional to the amount lost during administration of the drug. Another factor affecting the difference in sodium loss in the two dogs was probably the difference in the amount of ammonia formation.

The total anion excretion was quite large and was undoubtedly largely balanced by ammonia. Although ammonia was not directly determined, the calculated total represents a major portion of the cation block, particularly in Figure 5. Chronic oral administration of ammonium thiosulfate apparently stimulates the ammonia-producing mechanism of the kidney. Thus part of the value of this drug as a remover of fixed base is vitiated. However, the fact that both of these dogs lost weight during the period of drug administration is evidence that the drug was effective in removing intrinsic body base and water.

The marked base saving due to ammonia production in these chronic experiments is in contrast to the marked sodium loss during the short intravenous administrations. Apparently significant stimulation of the ammonia-producing mechanism does not take place within a few hours, but increases rapidly in the course of three days.

There was increased renal tubular reabsorption of chloride during the first two to three days of drug administration at a time when sulfate excretion rose to levels representing a six to ten fold increase over the

base line control excretion. This illustrates the phenomenon of increased reabsorption of chloride in the presence of a large increment of sulfate. Chloride excretion subsequently rose as sulfate excretion decreased at the end of the experiment period.

Contrasting with the very low phosphate excretion observed in the intravenous experiments, phosphate excretion rose sharply in these dogs. This is particularly evident in Figure 5 where the 24 hour total for phosphates is double that of the control period. A post-experiment suppression of phosphate excretion also occurred.

The increased phosphaturia can be partially correlated with the rise in potassium excretion although the latter is of greater magnitude. Phosphaturia in response to the rapid development of acidosis particularly following the administration of acid or acid producing substances is an old observation (17). Rappoport and coworkers have extended this observation by identifying diphosphoglycerate, an organic acid soluble phosphorus in blood cells, as the probable source of part of the increased inorganic phosphaturia (18). It is possible that the decomposition of diphosphoglycerate in the clood cell in response to acidosis is similar to processes occurring in other tissues.

DISCUSSION

The results obtained after administration of ammonium thiosulfate are similar in many respects to the effects of other ammonium salts of inorganic acids. The loss of sodium and potassium with increase in urine output and loss of body weight are the effects desired therapeutically when these salts are used as diuretics in patients with edema.

The early studies of Blum, Haldane, Keith and Gamble (19, 20, 21, 22, 23) revealed the mechanism of diuretic action of ammonium chloride, calcium chloride and ammonium sulfate. Ammonium nitrate has been used by Keith and others (24, 25, 26) but abandoned because of cyanosis and methemoglobinemia due to the reduction of some nitrate to nitrite.

The effectiveness of ammonium salts as diuretics or "base-removers" has been shown to be limited mainly by the capacity of the kidney to secrete ammonia, thereby saving base. More loss of base occurs at the beginning of administration because ammonia production is slow in starting and does not reach a maximum for three days in the normal

kidney. In damaged kidneys, the loss of base is greater due to failure to produce ammonia (27, 28). Ammonium thiosulfate stimulates ammonia production in a similar manner in the dog.

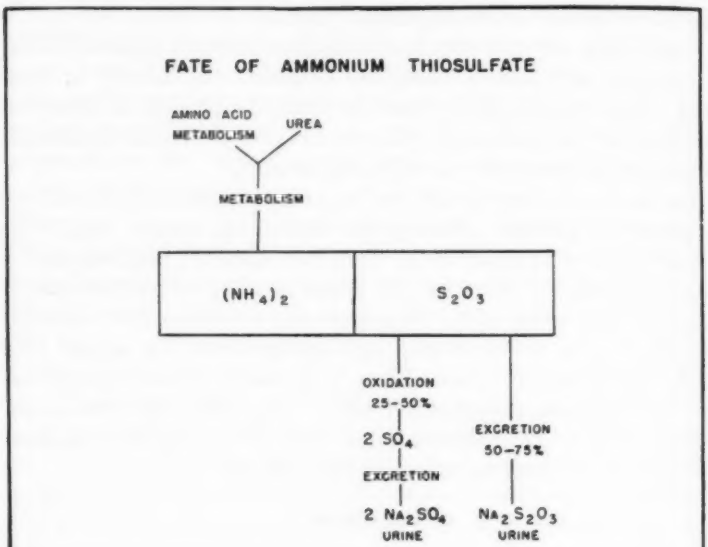

TABLE OF APPROXIMATE EQUIVALENTS

GMS	MEQ.	CC. OF EXTRACELLULAR FLUID CONTAINING EQUIVALENT AMOUNT OF NA
1 GRAM $(NH_4)_2$ S_2O_3	14	100
0.5 GRAM $(NH_4)_2S_2O_3$ AS 2 So_4	14	100

FIG. 7

Toxic effects have been attributed to the "acid producing" salts. Besides acidosis and dehydration produced by prolonged administration, minor toxic symptoms have been noted. Calcium chloride and

the ammonium salts of chloride, sulfate and nitrate produce some nausea and vomiting. Occasional vomiting occurred in our dogs after several days on large doses of ammonium thiosulfate.

The thiosulfate ion has two properties which are unique and different physiologically from the anions of other diuretic ammonium salts. First, thiosulfate is the only known inorganic electrolyte which is not reabsorbed by the renal tubules so that in both dogs and humans it is as rapidly excreted as any electrolyte can be, assuming that no inorganic electrolytes are secreted by the renal tubule. Thiosulfate, therefore, has the advantage as a "base-remover" that the rapidity of excretion is governed only by the rate of glomerular filtration after intravenous administration or after absorption from the gut. Like other acid salts its effectiveness is limited by the capacity of the kidney to secrete ammonia.

Another property of thiosulfate as an "acid salt diuretic" is derived from the process of conversion of some thiosulfate to sulfate, as illustrated in Figure 7. In dogs about 25% of intravenously and 50% of orally administered thiosulfate is converted to sulfate. Since one thiosulfate ion upon oxidation yields two sulfate ions, the potential base removing power of thiosulfate is doubled by the conversion. Furthermore the excess sulfate is excreted almost as rapidly as thiosulfate. The rapid excretion of sulfate can be seen in the charts and is confirmed by the fact that during thiosulfate excretion enough sulfate was recovered to account for the portion of thiosulfate which was oxidized. Rapid excretion of excess sulfate by the kidney has been described by Winkler after injections of sodium sulfate (29).

SUMMARY

Adult female dogs were given ammonium thiosulfate orally and intravenously to determine the effect on electrolyte excretion of an anion which is not reabsorbed by the renal tubules.

After a single intravenous injection of ammonium thiosulfate, approximately three fourths of the thiosulfate was recovered in the urine within three hours and the remaining one fourth was recovered as sulfate.

After a single oral dose of ammonium thiosulfate half of the thiosulfate was recovered in the urine and half as sulfate within seven hours.

The rapid excretion of thiosulfate after single doses is accompanied by a large increased sodium and slightly increased potassium excretion. With repeated doses less sodium is lost and larger amounts of ammonia are excreted. After single doses the excretion of chloride and phosphate is very low; but with repeated doses there is low excretion of chloride and a marked increase in phosphate excretion.

Increases in urine flow occurred regularly and followed the pattern of increased total base excretion. With repeated doses there was weight loss.

Continuous administration intravenously for six hours caused death with a low serum sodium and a high serum potassium.

Some vomiting occurred with large repeated oral doses in dogs.

BIBLIOGRAPHY

(1) Nyiri, W.: Uber die Thiosulfatprobe eine neue methode der nierenfunktionsprufung. Klin. Wchnschr., **2**(1): 204, 1923.

(2) Gilman, A., Philips, F. S., and Koelle, G. S.: The Renal Clearance of Thiosulfate with Observations on its Volume Distribution. Am. J. Physiol., **146:** 348, 1946.

(3) Newman, E. V., Gilman, A., Philips, F. S.: The Renal Clearance of Thiosulfate in Man. Bull. Johns Hopkins Hosp., **79:** 229, 1946.

(4) Barnes, R. B., Richardson, D., Berry, J. D., and Hood, R. L.: Flame Photometry, a Rapid Analytical Procedure. Industrial and Engineering Chemistry, Analytical Edition, **17:** 605, 1945.

(5) Hald, Pauline M.: The Flame Photometer for the Measurement of Sodium and Potassium in Biological Materials. J. Biol. Chem., **167**: 499, 1947.

(6) Howard, J. E., and Bigham, R. S., Jr.: Minutes of the Conference on Metabolic Aspects of Convalescence, New York. Josiah Macy, Jr. Foundation, Eleventh Meeting, Oct. 15–16, 1945.

(7) Harvey, S. C.: The Quantitative Determination of Chlorides in the Urine. Arch. Int. Med., **6:** 12, 1910.

(8) Volhard, J.: Die Silbertitrirung with Schwefelcyanommonium. Z. Anal. Chem., **17:** 482, 1878.

(9) Folin, O.: On Sulphate and Sulphur Determinations. J. Biol. Chem., **1:** 131, 1905.

(10) Fiske, C. H., and Subbarrow, Y.: The Colorimetric Determination of Phosphorus. J. Biol. Chem., **66:** 375, 1925.

(11) Albanese, A. A.: Determination of Ammonium in the Urine. J. Lab. & Clin. Med., **29:** 447, 1944.

(12) Kock, F. C., and McMeekin, T. L.: A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia. J. Amer. Chem. Soc., **46:** 2066, 1924.

(12a) BUELL, M. U.: Personal Communication.
(13) GENTZKOW, C. J.: An Accurate Method for the Determination of Blood Urea N_2 by Direct Nesslerization. J. Biol. Chem., **143:** 531, 1942.
(14) VAN SLYKE, D. D., AND STADIE, W. C.: The Determination of Gases of the Blood. J. Biol. Chem., **49:** 1, 1921.
(15) DARROW, D. C.: The Retention of Electrolyte during Recovery from Severe DEHYDRATION due to Diarrhea. J. Pediat., **28:** 515, 1946.
(16) FINCH, C. A., SAWYER, C. G., FLYNN, J. M.: Clinical Syndrome of Potassium Intoxication. Am. J. Med., **1:** 337, 1946.
(17) FORBES, E. B., AND KEITH, M. H.: A Review of the Literature of Phosphorus Compounds in Animal Metabolism. Wooster, Ohio Agricultural Experiment Station, Technical Series Bull., **5:** 510, 1914.
(18) GUEST, G. M., AND RAPPOPORT, S.: Organic Acid-Soluble Phosphorus Compounds of the Blood, Physiol. Rev., **21:** 410, 1941.
(19) BLUM, L., AUBELL, E., AND HAUSKNECHT, R.: L'Action Diuretique des sels de Calcium dans les Oedemes Generalises. Bull. et mem. Soc. Med. d. Hop. de Paris, **45:** 1561, 1921.
(20) HALDANE, J. B. S.: Experiments on the Regulation of the Blood's Alkalinity. J. Physiol., **55:** 265, 1921.
(21) HALDANE, J. B. S., HILL, R., AND LUCH, J. M.: Calcium Chloride Acidosis. J. Physiol., **57:** 301, 1923.
(22) KEITH, N. M., AND WHELAN, M.: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds. J. Clin. Invest., **3:** 149, 1926.
(23) GAMBLE, J. L., BALCKFAN, K. D., AND HAMILTON, B.: A Study of the Diuretic Action of Acid Producing Salts. J. Clin. Invest., **1:** 359, 1925.
(24) KEITH, N. M., WHELAN, M., AND BANNICK, E. G. Diuretic Action of Nitrates and their Use in the Treatment of Dropsy. Tr. Assoc. Am. Phys., **43:** 288, 1928.
(25) KEITH, N. M., AND EUSTERMAN, G. B.: Transient Methemoglobinemia following Administration of Ammonium Nitrate. M. Clin. North. Amer., **12:** 1489, 1929.
(26) TARR, L.: Transient Methemoglobinemia due to Ammonium Nitrate. Arch. Int. Med., **51:** 38, 1933.
(27) PALMER, W. W., AND HENDERSON, L. J.: A Study of the Several Factors of Acid Excretion in Nephritis. Arch. Int. Med., **16:** 109, 1915.
(28) VAN SLYKE, D. D., LINDER, G. C., HILLER, A., LEITER, L., AND MCINTOSH, J. F.: The Excretion of Ammonia and Titratable Acid in Nephritis. J. Clin. Invest., **2:** 255, 1926.
(29) WINKLER, A. W., PETERS, J. P., AND ASSOCIATES: Duncan's Diseases of Metabolism. W. B. Saunders Co., Philadelphia and London, 1942, page 292.

THE USE OF TELEVISION IN SURGICAL OPERATIONS

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Television of surgical operations was used for the first time at the Johns Hopkins Hospital on 27 February 1947. The experiment was dramatically successful.

The customary method of demonstrating surgical operating technique to students and to visiting doctors or nurses has proved unsatisfactory for two reasons. In the first place, the observers cannot see the operating field properly; in the second place, these observers bring contamination into the operating room. Except for two or three people who stand on raised platforms immediately behind the operator, the demonstration of an operation is almost never satisfactory. To a class in surgery an operative clinic is almost a complete waste of time. Also it is a well established fact that the number of pathogenic organisms which may be cultured from the air of an operating room is in direct proportion to the number of people in the room even though these people are gowned, capped, and masked, and that the bacteria gain their entrance into the room mainly in the nose and throat passages of the people present. In order to overcome these difficulties in clinical instruction in surgery, the authors conceived the idea of employing television. When the Radio Corporation of America was consulted on the subject they immediately dispatched a representative to Baltimore from Camden, New Jersey, to consult about the proposition.

A stimulus to those studying the possibilities was the projected biennial meeting of the Johns Hopkins Medical and Surgical Association at which 750 members were scheduled to attend. Since a large percentage of these are surgeons, and since many others are interested in the newer surgical techniques, especially the so-called "blue baby" operations on the heart, it was foreseen that the operating rooms would be swamped with visitors. Accordingly, a target date was set with the Radio Corporation of America to make every possible effort to secure and set in place the necessary television equipment for use on the days of the meeting, 28 February–1 March, 1947.

Besides the procurement of this equipment there were certain engineering problems to be settled. These were the construction of a de-

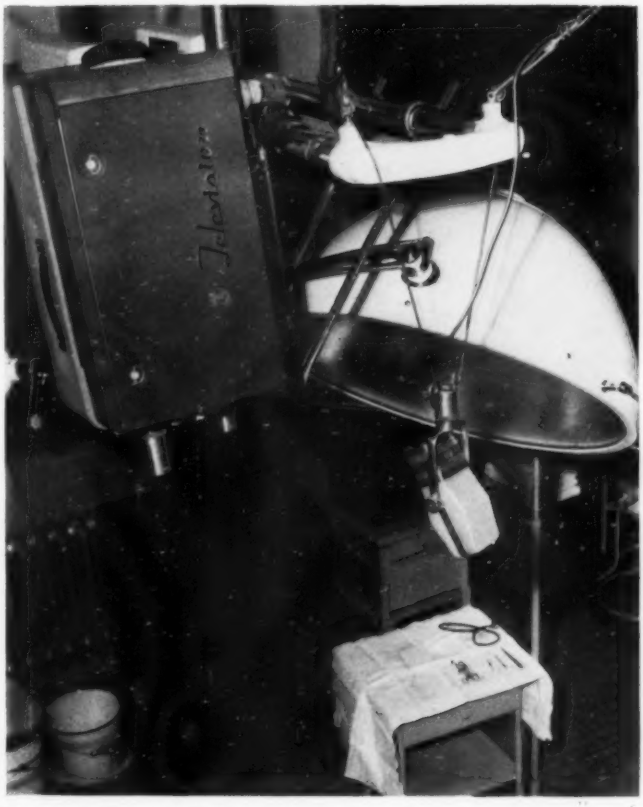

FIG. 1. TELEVISION CAMERA MOUNTED ON OPERATING ROOM CENTRAL LIGHT FIXTURE

Distance of camera above operating room table 4½ feet. Microphone apparatus in place

vice to hang the camera from the central overhanging electric light fixture in the operating room and the installation of two temporary single phase, alternating current, 30 ampere, 110 volt circuits, one for

the camera and the electronic transmission, and the other for the projectors.

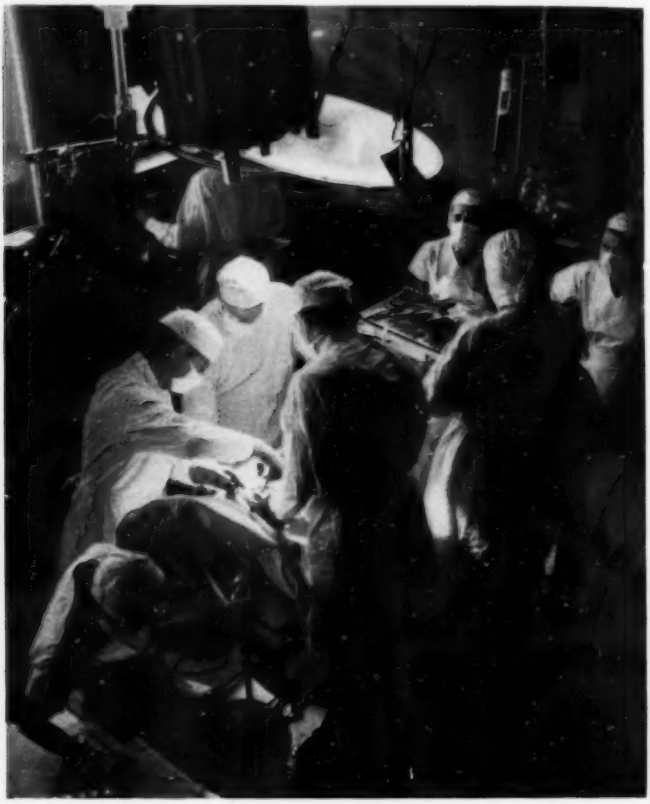

FIG. 2. CHEST OPERATION FOR PULMONIC STENOSIS

Five operations were transmitted to ten television receivers in four different classrooms on two separate floors at distances of approximately 200 feet from the operating room. At the same time through a loud speaker system the surgeon described each operation step by step as he performed it.

Four of the operations were performed on the heart, the fifth on the sympathetic nerve trunk along the vertebral column. The first two operations were performed by Dr. Alfred Blalock using the technique

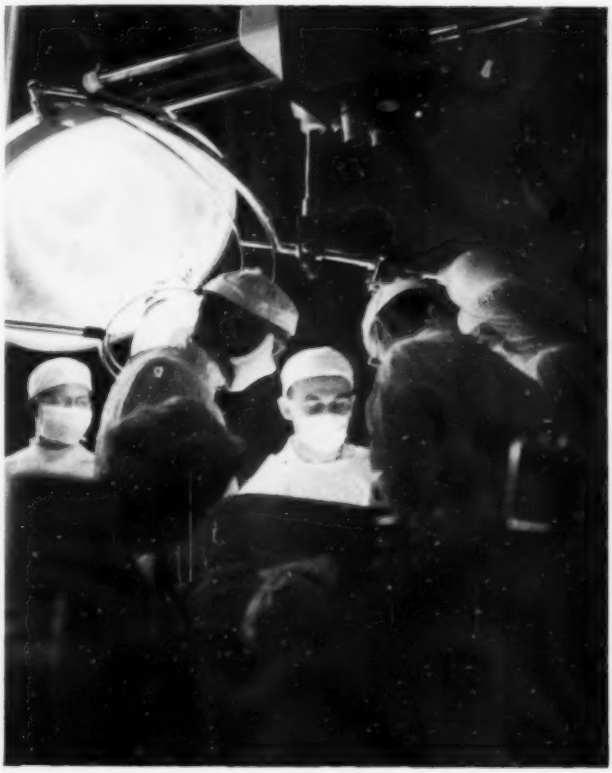

FIG. 3. ABDOMINAL OPERATION TO SEVER LUMBAR SYMPATHETIC TRUNK

devised by him and Dr. Taussig to increase the insufficient amount of blood reaching the lungs because of congenital stricture of the pulmonary artery, the so-called "blue baby" operation. The third operation was performed by Dr. I. R. Trimble when the lumbar sympathetic nerve trunk was resected along the vertebral column in order to improve the circulation in the leg. Dr. H. W. Scott, Jr., performed the

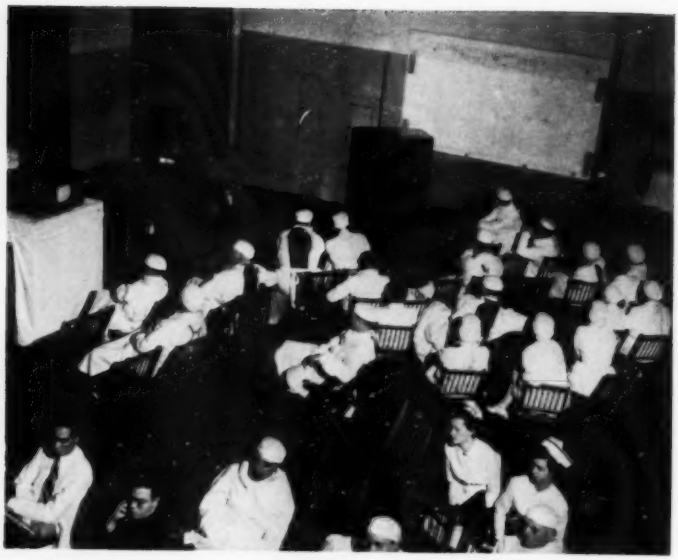

FIG. 4

FIG. 5

FIGS. 4 AND 5. SPECTATORS VIEWING TELEVISION SCREENS

fourth operation, ligating a congenital abnormal opening in the great vessels coming off the heart, the patent ductus arteriosus. Dr. W. P. Longmire, Jr., performed the fifth operation, which was again the Blalock-Taussig operation on the heart.

Two television cameras were in constant use. Before operations were commenced the camera recording the operating field, which was clamped to the overhead operating light 4½ feet above the operating table, was accurately focused. So sharp was the image that when a dollar bill was placed on the operating table for the purpose of focusing the estimated distance of the operating field from the camera, the serial numbers on the bill could be clearly read on the projection screens. A 135 mm. focal length lens gave a field of view of 8½ x 11½ inches at this distance. Each step in the operations was clearly recorded by television—the incision, the clamping of small bleeding vessels, the delicate suturing with fine silk of the blood vessels as the subclavian and pulmonary arteries were united, the demonstration of fine nerve fibers. The pictures were registered in black and white since technicolor is still in its experimental stage in television.

The second television camera was installed in the gallery of the operating room to show a general view of the activity in the operating room. From the small control room pictures which were taken by this second camera were at times flashed on the projection screens, alternating with camera number one which was recording a close-up view of the operative field only.

It is believed that this experiment in television has proved conclusively that demonstration of and instruction in surgical operations to a group of more than three or four people can be best accomplished by the use of television and that future operating room construction will be greatly modified because of the introduction of this method of teaching.

The authors are indebted to Mr. W. L. Lawrence and Mr. N. S. Bean and the crew of advisers and technicians from the Radio Corporation of America, to Miss Elizabeth W. Sherwood, Head Nurse of the General Operating Rooms at the Johns Hopkins Hospital, and to her staff of nurses, and to Mr. W. D. Witter, Chief Engineer of the Johns Hopkins Hospital, and his staff.

PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE[1]

IV. Measurements of the Circulation in Five Selected Cases

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In the preceding two papers of this series circulatory measurements of the tetralogy of Fallot and of Eisenmenger's complex have been presented (1, 2). It is the aim of the present communication to describe the diagnostic value of these physiological studies when applied to a variety of clinical problems.

The various procedures employed in these studies of congenital heart disease have been reported in detail in the first paper of this series (3). Most of the data were obtained by applying the Fick principle. Blood gas values substituted in the Fick equation were obtained by catheterization of the heart chambers and great vessels, by arterial puncture, and by analysis of respiratory gases. In presenting the results of case studies in these reports a number of terms describing blood volume flows have been employed. For purposes of clarity they will be redefined at this time.

Pulmonary capillary flow, the amount of blood flowing through the lung capillaries per unit time, is derived from the formula:

$$1.\quad \text{Pulmonary capillary flow (ml. per min.)} = \frac{\text{CO}_2\text{ output (ml. per min.)}}{\text{CO}_2\text{ content of blood entering pulmonary capillaries (vol. per cent)} - \text{CO}_2\text{ content of blood leaving pulmonary capillaries (vol. per cent)}} \times 100$$

Pulmonary artery blood flow, the volume of blood flowing through the pulmonary valve into the pulmonary artery, is calculated from the formula:

$$2.\quad \text{Pulmonary artery flow (ml. per min.)} = \frac{\text{O}_2\text{ intake (ml. per min.)}}{\text{O}_2\text{ content of pulmonary vein blood (vol. per cent)} - \text{O}_2\text{ content of pulmonary artery blood (vol. per cent)}} \times 100$$

[1] This work was supported by a grant from the Commonwealth Fund.

When the oxygen content of pulmonary vein blood cannot be directly determined, a figure based on the assumption that pulmonary vein blood is fully oxygenated is substituted in this equation. Moreover, when a blood sample is not procurable from the pulmonary artery, the oxygen content of blood taken from the outflow tract of the right ventricle is likewise substituted for pulmonary artery blood in the equation.

The collateral pulmonary blood flow is that portion of the capillary flow to the lungs contributed by sources other than the pulmonary artery. Hence:

3. Collateral pulmonary blood flow (ml. per min.) =
Pulmonary capillary flow (ml. per min.) − pulmonary artery flow (ml. per min.)

The systemic blood flow, the volume of blood coursing through the peripheral blood vessels, is expressed by the formula:

$$4.\ \text{Systemic flow (ml. per min.)} = \frac{\text{O}_2\text{ intake (ml. per min.)}}{\text{O}_2\text{ content of peripheral arterial blood (vol. per cent)} - \text{O}_2\text{ content of right auricular blood (vol. per cent)}} \times 100$$

The intracardiac shunt is the volume of blood per unit time shunted from one side of the heart to the other through septal defects. The shunt is designated "right to left" or "left to right" depending on the predominant direction in which the volume of blood is shifted. The formulae for calculation of the shunt are:

5. Intracardiac shunt, right to left (ml. per min.) =
Systemic blood flow (ml. per min.) − pulmonary artery blood flow (ml. per min.)

or,

6. Intracardiac shunt, left to right (ml. per min.) =
Pulmonary artery blood flow (ml. per min.) − systemic blood flow (ml. per min.)

The effective pulmonary blood flow is the volume of mixed venous blood which, after its return to the right auricle, ultimately reaches the pulmonary capillaries. It is derived from the equation:

$$7.\ \text{Effective pulmonary blood flow (ml. per min.)} = \frac{\text{O}_2\text{ intake (ml. per min.)}}{\text{O}_2\text{ content of pulmonary vein blood (vol. per cent)} - \text{O}_2\text{ content of right auricular blood (vol. per cent)}} \times 100$$

Here again the assumption is made that pulmonary vein blood is fully oxygenated when blood cannot be obtained directly from that vessel.

In addition to the procedures already referred to, the standard exercise test described in a previous publication (3) was employed in these studies.

For presentation in this paper there have been chosen five cases of congenital heart disease. In three of these the anatomical diagnoses suggested by the physiological tests were confirmed at postmortem examination. In the remaining two cases the diagnoses provided by the physiological procedures were confirmed at operation. In the case

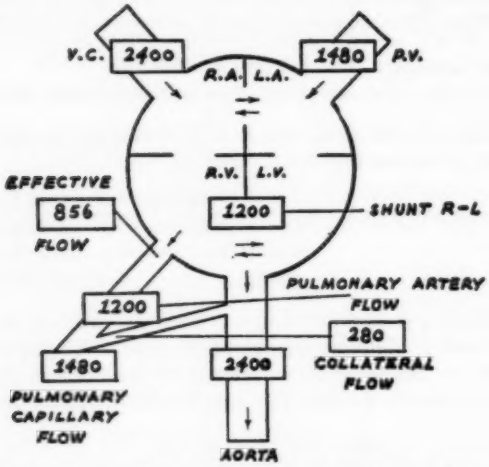

FIG. 1. illustrates the results from the physiological procedures in Case 1 (C. H.). Pulmonic stenosis is indicated by the volume of blood flow through the pulmonary artery which is 1200 cc. The presence of an interauricular septal defect is suggested by the gradient in O_2 content between vena caval and auricular bloods (Table II). Similarly the presence of an interventricular septal defect is demonstrated by the gradient between auricular and ventricular bloods (Table II). The volume of the intracardiac shunt directed from right to left is probably made up of auricular and ventricular components. Since the effective blood flow to the lungs is 344 cc. less than the pulmonary artery flow there is evidence for left to right mixing of blood in the heart chambers.

histories only facts relevant to an understanding of the underlying physiological abnormalities will be listed.

CASE HISTORIES

Case 1, C. H., was a fifteen year old youth first seen in March of 1946. His color at birth was momentarily blue but soon became normal. Although development was noticeably retarded, it was not until he was nineteen months old that

his parents learned he had heart disease. Following an attack of whooping cough, at two years of age, cyanosis became apparent with exercise but was not pronounced until the age of four. The course since that time had been one of progressive cyanosis and limited activity. Dyspnea had become extreme in the two years before he was seen here. At the time of admission his exercise tolerance was restricted to walking a distance of one hundred yards.

When examined he was a tall thin boy. Generalized cyanosis and clubbing of the fingers were extreme, with the cyanosis more evident in the upper extremities. A right dorsal scoliosis was accompanied by prominence of the left side of the chest anteriorly. A marked systolic thrill could be felt at a maximum in the third left intercostal space. The heart sounds were of good quality and the rhythm regular. Three distinct systolic murmurs were heard: a high-pitched whistling murmur at the base, a rough rumbling murmur over the precordium heard best in the third left intercostal space, and a systolic blow at the apex. Blood pressures in the arms and legs were equal at 125/100 mm. Hg. The remainder of the physical examination was not unusual.

Under the fluoroscope the heart was globular, rotated, and enlarged. The aorta was increased in outline and descended on the right side. The pulmonary conus was not prominent. In the left anterior oblique position the right ventricle bulged forward unduly. The pulmonary window was not clear. Lung markings were increased but active pulsations in the lung fields were not observed.

Electrocardiographic tracings with the standard leads revealed a normal sinus mechanism with sinus arrhythmia, and right deviation of the electrical axis. Routine laboratory tests resulted in a red blood cell count of 9.36 millions, a hemoglobin of 26 grams (Sahli), a hematocrit of 75 per cent, a non-protein nitrogen of 66 mgms. per cent, and a peripheral arterial O_2 saturation of 63 per cent.

The clinical opinion was that the heart was rotated and that the aorta descended on the right. A single ventricle was suspected. Without definite evidence for pulmonary stenosis, operation could not be attempted. For this reason the patient was referred to the laboratory for physiological studies.

Results of physiological procedures: Some of the significant data obtained are illustrated in Figure 1. Pulmonary capillary blood flow calculated from the figures in Table I was 1480 cc.[2], less than half the average normal cardiac index of 3000 cc. (4). Two catheterizations of the heart were performed (Table II). On March 14th the catheter introduced in the left arm entered the left side of the heart. The first auricular blood sample taken from the left border of the heart had an O_2 saturation of 94 per cent, thereby indicating that it originated close to the entry of a pulmonary vein. With the catheter passing across the

[2] In this paper all figures for volume of blood flow are expressed in terms of cc. per minute per square meter of body surface.

upper border of the heart shadow and extending into the right pulmonary field, a second blood specimen was found to be 95 per cent saturated with oxygen. In view of the catheter position and the saturation of the blood sample it seemed probable that the pulmonary vein had been catheterized.

During the second catheterization through the right antecubital vein the catheter again entered the left side of the heart (Table II). A blood sample with 18.2 vols. per cent O_2 was thought to originate from the right auricle. Specimens taken from various ventricular locations contained from 19.8 to 22.0 vols. per cent O_2. There was close corre-

TABLE 1

Data Obtained from Equilibration Method for Determination of Pulmonary Capillary Flow

NO.	DATE	SUBJ.	AGE	SEX	SURF. AREA M^2	CO_2 PROD.	CO_2 CALC.	R. Q.	MIN. VOL.	CO_2 INCOMING BLOOD			CO_2 OUTGOING BLOOD			PULM. CAPILLARY FLOW
										%	Tension	Vols.	%	Tension	Vols.	
						cc./min.			L/min.		mm. Hg.	%		mm. Hg.	%	L/min./M^2
1	3/14/46	C. H.	15	M	1.6	229	155	1.2	9.27	4.22	30.3	27.5	2.81	20.1	21.0	1480
2	5/20/46	R. A.	22	M	1.5	157	127	1.0	6.93	3.84	27.5	27.2	2.84	20.1	22.7	2390
3	11/25/46	J. S.	32	F	1.5	133		0.7	4.7	4.81	34.2	44.1	4.07	29.0	41.0	2860
5	1/27/47	W. G.	16	M	1.7	206		0.9	9.25	4.10	29.3	26.5	3.33	23.7	22.9	3280

spondence between the O_2 content of blood taken from the outflow tract of the right ventricle and that of the femoral artery (Table II).

In the absence of a representative sample for mixed venous blood, a circumstance occasioned by mixing of arterial and venous blood between the auricles, formulae for the calculation of systemic and effective pulmonary blood flows could not be applied. However, if the O_2 content of blood from the inferior cava were to be considered as approximating that of the returning mixed venous blood, a systemic blood flow of 2400 cc. and an effective pulmonary blood flow of 856 cc. could be derived by applying Formulae 4 and 7. Pulmonary artery blood flow utilizing the sample from the outflow tract of the right ventricle was 1200 cc., approximately half the normal cardiac output (4). The intra-cardiac shunt directed from right to left was 1200 cc. and the collateral circulation to the lung 280 cc. (Formula 3).

Comment: In spite of the many anomalies in this heart, there were found the necessary prerequisites for operation. Pulmonary capillary and pulmonary artery blood flows were reduced to some 1480 and 1200 cc. respectively, and of these amounts slightly more than half was venous blood. (The effective pulmonary blood flow was 856 cc.) (Table II) (Fig. 1).

The predominating direction of the intracardiac shunt, right to left, was similar to that found in the tetralogy of Fallot (1). Finally with the peripheral blood O_2 saturation at 69 per cent, it appeared likely that the effective blood flow to the lungs could be increased by constructing a "ductus" at operation.

Much of the information concerning the character of the congenital defects in this case was secured preoperatively by observation of the catheter movements within the heart. In this fashion, rotation of the heart, abnormal entry of the venae cavae, a single auricle, and a single ventricle were all suspected. The O_2 content of blood from the heart chambers provided additional evidence for the presence of septal defects. The O_2 content of blood from the inferior vena cava was lower than any of the auricular blood samples, suggesting that admixture of oxygenated and venous blood was occurring in the auricles (Table II). The same conclusion was drawn from the range of O_2 contents in blood from the ventricles. Close correspondence between the O_2 contents of blood from the outflow tract of the right ventricle and the femoral artery indicated that there was a functional single ventricle (Table II).

The predominant direction of the intracardiac shunt was right to left but there was concomitant shunting of blood in a left to right direction. Evidence for the latter was the observed volume of effective pulmonary blood flow which was 400 cc. less than the pulmonary artery flow and 620 cc. less than the pulmonary capillary flow (Table II).

The calculated collateral blood flow to the lungs was less than would have been expected from findings at operation and necropsy. In this instance the discrepancy may have lain in an unduly large calculated volume for pulmonary artery blood flow. The possibility of error in the calculation of pulmonary artery blood flow, in the presence of large collateral circulation to the lung, has already been discussed (3).

Procurement of fully oxygenated blood from the pulmonary vein in this case eliminates the possibility of a lung factor as being responsible

TABLE II

Data Obtained from Catheterization of the Heart

NO.	DATE	SUBJ.	AGE	SEX	SURF. AREA M^2	O_2 CONSUMED	CO_2 PRODUCED	R.Q.	MIN. VOL.	B.M.R.	O_2 VOLUMES PER CENT					FEMORAL ARTERY O_2			FLOWS/M^2		EFFECTIVE FLOW	SHUNT
											V.C.	R.A./L.A.	R.V.	P.A.	P.V.	Content	Capacity	Saturation	P.A.	Systemic		
						cc./min.	*cc./min.*		*L/M*												*cc./min./M^2*	*cc./min./M^2*
1.	3/14/46	C.H.	15	M	1.6	154	240	1.9	12.8	−40		31.3			32.0*	23.3	33.6	69.3				
	3/18/46					195	153	0.8	6.22	−25	17.9	18.2	19.8 22.0			22.9			1200	2400	856	1200
2.	5/23/46	R.A.	22	M	1.5	157	157	1,0	6.93	−25		23.1	26.7		33.5	28.9	35.2	82.0	1590	1850	1035	260
3.	11/27/46	J.S.	32	F	1.5	141	126	0.9	5.04	−24		13.0	12.5	14.4	18.5	18.5	19.8	93.5	2290†	1710	1710	0
4.	1/18/47	M.B.	18	F	1.3	127	127	1.0	8.14	−28		12.5	12.5	15.4	30.5	16.4	32.4	51.2	615	2400	517	1785
5.	1/28/47	W.G.	16	M	1.7	235	203	0.8	10.2	− 5	16.4	17.3 to 21.4	19.2		29.7	24.3	31.2	78.5	1280	1709	1014	429

* Direct Determination
† Pulmonary Capillary flow determined directly

TABLE III

Results Obtained from the Standard Exercise Test

NO.	DATE	SUBJ.	AGE	SEX	SURF. AREA M^2	VENTILATION	CO_2		O_2		R.Q.	ARTERIAL BLOOD			
							cc. per M^2	cc. per L.V.	cc. per M^2	cc. per L.V.		O_2	CO_2	Cap.	Sat. %
						Liters/min./M^2						Vols. %	Vols. %	Vols. %	
3.	11/29/46	J.S.	32	F	1.5	Rest 3.36	84.5	25.2	94.0	25.9	0.88	18.5	41.0	19.8	93.5
						Exercise 8.05	236.0	29.2	359.0	44.4	0.66	17.4	40.5	19.8	88.2
4.	1/20/47	M.B.	18	F	1.3	Rest 7.15	111.0	15.5	150.0	20.9	0.75	16.4	28.0	32.1	51.2
						Exercise 11.1	157.0	14.3	176.0	16.0	0.81	11.6	36.0	32.1	37.2
5.	1/28/47	W.G.	16	M	1.7	Rest 5.87	116.0	19.9	135.0	23.0	0.85	24.3	28.6	31.2	78.5
						Exercise 8.25	134.0	16.3	107.0	13.0	1.25	2.0	42.5	31.2	6.4*

* Venous blood

for the symptom of cyanosis at rest. This finding is in agreement with others previously reported from this laboratory. Consequently peripheral O_2 unsaturation and cyanosis in this case are the result of shunting of blood from the venous to the arterial side of the circulation.

Following upon the performance of the physiological tests, operation was performed on June 6, 1946. A good many collateral blood vessels were encountered in the mediastinum. One of the venae cavae and the azygos vein lay on the left side of the mediastinum. A large left pulmonary artery was dissected out but pulsations in it were minimal. An end-to-side anastomosis between the left subclavian and left main pulmonary arteries was effected. After closure of the chest the pulse weakened and the patient succumbed within an hour.

At postmortem examination the heart was greatly enlarged, dilated and completely rotated so that the right ventricle lay on the left side. The superior vena cava and the pulmonary veins entered the auricle to the left of the interatrial septum while the inferior cava entered on the right. In essence there was a single functioning auricle because of a patent foramen ovale and an auricular septal defect 3 cm. in diameter. The ventricular walls were hypertrophied. The pulmonary artery arose from a chamber which was an anterior projection of the left ventricle. A white scarlike tissue almost occluded the pulmonary conus 5 cm. below a normal pulmonary valve. The aorta, arising chiefly from the left ventricle, straddled a 4 cm. defect in the interventricular septum.

Case 2, R A., was a twenty-two year old man, referred to the laboratory for study in May of 1946. At birth his color was blue and had remained so ever since. He always had had shortness of breath intensified by exertion and relieved by the assumption of a squatting position. During his early years there were many brief syncopal attacks which diminished in number as he grew older and finally ceased by the time he was fifteen years old. Despite the limitations of his illness he successfully completed secondary schooling. Six weeks before entry a coughing spell was said to have resulted in a hemoptysis. When seen in this hospital his exercise tolerance was limited to walking a distance of one city block.

On physical examination he appeared frail and underdeveloped for his age. Cyanosis of the skin, mucous membranes, and nail beds, and clubbing of the digits were immediately apparent. The chief positive findings were in relation to the heart examination. The precordium appeared normal. Over the lower end of the sternum on the left a faint systolic thrill was palpated. The heart

sounds, rate and rhythm were all normal but a moderately harsh systolic murmur could be heard. Its maximum intensity was at the lower left border of the sternum. A diastolic murmur was not found. Blood pressures in the arms and legs were the same at 100/80 mm. Hg. In the abdomen the liver edge was felt 1½ fingers breadth below the costal margin. The remainder of the examination was uneventful.

Under the fluoroscope the heart was not enlarged. There was a sharp concavity in the region of the pulmonary conus in the anteroposterior position. In the left oblique position the pulmonary window was clear. Although there were no pulsations in the lung fields themselves, minimal pulsations were present in the right hilar area. The aorta descended on the left side.

Electrocardiographic tracings with standard leads showed a normal sinus mechanism and deviation of the electrical axis to the right. Laboratory tests revealed a red blood cell count of ten millions, a hematocrit of 84 per cent, a hemoglobin of 21.9 gms. (Sahli), a non-protein nitrogen of 65 mgms. per cent, and a peripheral arterial O_2 saturation of 82 per cent.

The history and physical findings in this case were those of the tetralogy of Fallot. It was believed that physiological studies would confirm the diagnosis established clinically.

Results of physiological studies: Some of the significant data derived from the tests are portrayed in Figure 2. Pulmonary capillary blood flow was reduced to 2390 cc. (Table I). Results from the heart catheterization revealed the right ventricular blood to be 3.6 vols. per cent higher in O_2 content than that of the auricle (Table II). Pulmonary artery and effective pulmonary blood flows were 1590 cc. and 1035 cc. respectively. The collateral blood flow to the lungs was 800 cc. (Formula 3), and the intracardiac shunt directed from right to left was 260 cc. (Table II). Systemic blood flow was 1850 cc.

Comment: The circulatory measurements pointed to the diagnosis of tetralogy of Fallot. The pulmonary artery blood flow, half the average normal, spoke for stenosis of the artery. The auriculo-ventricular difference in blood O_2 content indicating mixing of blood between the ventricles suggested the presence of an interventricular septal defect.

An unusual feature of the results was the volume of the intracardiac shunt, lower than most previously observed in the tetralogy of Fallot (1). Despite the small calculated shunt there was extensive mixing of blood through the septal defect as indicated by the auriculo-ventricular O_2 gradient. Although the overall direction of the intracardiac shunt was right to left, a comparison of effective with pulmonary artery blood flow indicated that there was left to right shunting as well (Table II).

The effective blood flow to the lungs was 555 cc. less than the pulmonary artery blood flow. Evidence for right to left shunting of blood was found in the peripheral arterial unsaturation of 82%. There was present then reciprocal mixing and shunting of blood between the two sides of the heart with a small right to left shunt predominating.

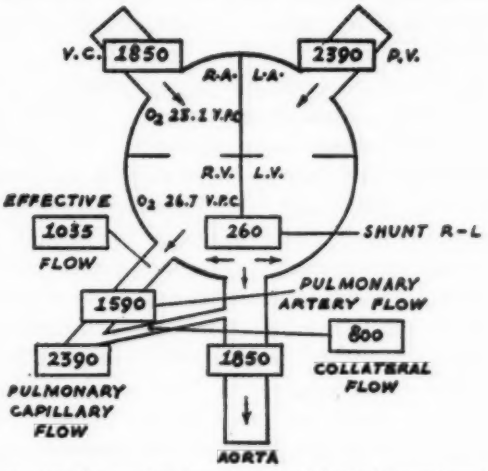

FIG. 2. illustrates the results from the physiological procedures in Case 2 (R A.). Pulmonic stenosis is indicated by the volume of blood flow through the pulmonary artery. The presence of an interventricular septal defect is suggested by the difference in O_2 content between auricular and ventricular bloods. The intracardiac shunt is small and directed toward the left. Evidence for left to right mixing of blood is the observation that the effective blood flow to the lungs is 555 cc. less than the pulmonary artery blood flow. These findings are typical for the tetralogy of Fallot.

The collateral circulation to the lungs was 800 cc. A third of the aortic output of 2650 cc., therefore, was diverted to the lungs through collateral blood vessels. The resulting decrease in peripheral blood flow to 1850 cc. may have had some bearing on the postoperative behavior of this patient. Upon the creation of an artificial ductus at operation there may have been a temporary further reduction in the volume of systemic blood flow below its original level. A sizable quantity of aortic blood, following the course of least resistance to the lung, was

made to short-circuit the periphery. Similar circulatory changes have been observed following the creation of an artificial ductus in dogs and in closure of the ductus in man during acute experiments by Eppinger, Burwell and Gross (5). The postoperative shocklike state shown by the patient under discussion may well have been part of the symptomatology of a markedly reduced peripheral blood flow and decreased venous return to the heart. Contributing to the picture was the blood loss at operation.

After completion of the special procedures, operation was performed on February 5, 1947. A moderate number of collateral blood vessels were seen in the mediastinum on the right side. The right pulmonary artery was relatively long, thereby confirming the preoperative fluoroscopic finding of hilar pulsations. The circumference of the artery was smaller than would have been expected for the patient's size. The pressure in it was low as measured with a saline manometer and pulsations were absent. An end-to-side anastomosis between the right subclavian and main right pulmonary artery was accomplished, after which a thrill was readily palpable. For two days postoperatively, the patient had persistent hypotension with the pressure never above 75/30 mm. Hg. He had anuria and moderate tachycardia. Toward the evening of the second day the patient became intensely cyanotic and soon expired.

At necropsy 400 cc. of bloody fluid were found in each pleural cavity. The heart was greatly enlarged with the right ventricular wall thicker than the left. The membranous portion of the interventricular septum had a moderate sized defect above which the aorta overrode both ventricles. Beyond the pulmonary conus, dilated in its lower half, there was stenosis at the pulmonary valve. The pulmonary artery widened beyond the valve and measured 2 cm. in circumference. The anatomical findings were those of the tetralogy of Fallot.

Case 3, J. S., was a thirty-two year old married female first seen in November of 1946. The onset of symptoms associated with the present illness occurred during her first and only pregnancy. In 1941, in the fourth month of pregnancy, she had experienced undue fatigue and shortness of breath, both of which became more marked as pregnancy progressed. A physical examination in the seventh month revealed signs thought to be characteristic of a patent ductus arteriosus. The remarkable aspect of these findings was their discovery for the first time in

1941 despite many previous examinations. The patient's pregnancy was completed in a normal fashion. Since that time she had experienced overwhelming fatigue and breathlessness on slight exertion. There had never been cyanosis, orthopnea, or ankle edema. Her symptoms had forced her to remain in bed a good part of the day, but it was suspected that part of her disability was due to worry about her heart.

When examined she was well nourished and developed. The chief physical findings centered about the heart where a faint diffuse systolic heave was seen anteriorly over the left chest. A continuous thrill with systolic accentuation could be felt over the precordium. At the apex the heart sounds were normal in quality and the rhythm was regular. The predominating sound on auscultation was a loud continuous machinery-like murmur, accentuated during systole, heard maximally in the second left intercostal space, and audible over most of the left chest anteriorly and posteriorly. A faint systolic murmur was heard in the apical area. The blood pressure was 115/65 mm. Hg. in both arms. The remainder of the physical examination was not remarkable.

An antero-posterior x-ray view of the chest revealed the cardiac silhouette to be normal in size and contour. Under the fluoroscope the heart contracted vigorously and the apex excursions were wide. There were no abnormalities of the pulmonic conus or aortic knob. Pulsations were not seen in the lung fields.

Electrocardiographic tracings taken with the standard leads and chest leads were within normal limits. A stethogram portrayed a murmur with maximum intensity early in systole, which continued through the second sound and the first half of diastole.

Because of the discovery of a characteristic ductus murmur for the first time during pregnancy and relatively late in life, as well as a disproportion between symptoms and physical findings, this woman was referred to the laboratory for further study.

Results of physiological studies: Some of the findings are illustrated in Figure 3. Results from the heart catheterization may be seen in Table II. The variation in O_2 content between auricular and ventricular blood was considered to be within the limits of error inherent in the catheterization technique (6). In calculating systemic blood flow, right auricular blood O_2 content was employed to arrive at a flow of 1710 cc. Formula 4 (Table II). This was some 1000 cc. below the average normal cardiac index (4). Systemic and effective pulmonary blood flows were equal in amount (Table II). In the absence of evidence for intracardiac shunting of blood it was assumed that pulmonary artery blood flow was equal to the systemic flow.

Pulmonary capillary blood flow determined by the CO_2 equilibration technique was 2860 cc. (Table I). Since Eppinger, Burwell and Gross

(5) have shown that complete mixture of arterial and venous blood in the smaller branches of the pulmonary artery occurs in patent ductus arteriosus, it was also possible to determine pulmonary capillary blood flow by catheterization of the pulmonary artery in the case under discussion. Employing the oxygen content of blood from the pulmonary

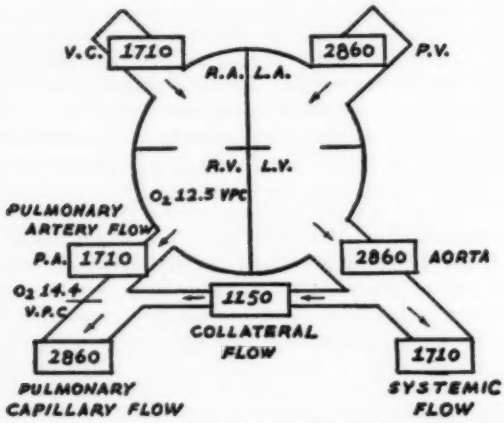

FIG. 3. illustrates the results from the physiological procedures in Case 3 (J. S.). Pulmonary capillary blood flow exceeds the pulmonary artery blood flow by 1150 cc., indicating that there is a large collateral circulation to the lungs via the ductus. The gradient in O_2 content between ventricular and pulmonary arterial bloods demonstrates that oxygenated blood is entering the pulmonary artery through the ductus. Despite an aortic output of 2860 cc. the systemic blood flow is only 1710 cc. This reduction in systemic blood flow is probably secondary to shunting of blood away from the aorta.

artery (Table II), the pulmonary capillary flow was found to be 2290 cc. Thus there was fairly close agreement between capillary blood flows determined by the CO_2 equilibration method and the catheterization technique (Tables I and II). The collateral blood flow to the lung calculated with Formula 3 was 1150 cc.

During catheterization of the heart the blood pressure in the right ventricle recorded with a Hamilton manometer was 33/10 mm. Hg. The pressure in the femoral artery was 150/90 mm. Hg., with a calculated mean pressure of 115 mm. Hg. This finding of an elevation in the

mean pressure (normal 90 mm. Hg) is contrary to the usual experience in large patent ductus where the pulse pressure is increased over the normal but the mean pressure reduced because of a lowered diastolic pressure (5).

Performance of the exercise test (Table III) resulted in a marked rise in the ratio, O_2 consumed per liter of ventilation. From this it was inferred that the effective blood flow to the lung increased normally with exercise.

Comment: The collateral blood flow to the lung through the ductus in this patient comprised 40 per cent of the left ventricular output and was responsible for the fact that the output of that ventricle was 1.5 times that of the right. Despite a relatively normal left ventricular output of 2860 cc., the volume of the peripheral circulation was only 1710 cc. A similarly decreased peripheral blood flow was observed by Eppinger, Burwell and Gross following the creation of an artificial ductus in dogs and before closure of a patent ductus in man (5). It was reasoned, therefore, that the reduced systemic blood flow observed in this patient was secondary to a large collateral flow to the lung contributed by the ductus.

It is interesting that the O_2 content of pulmonary artery blood was 1.9 vols. per cent higher than that of the right ventricle (Table II, Fig. 3). A gradient of this magnitude can be explained by admixture of oxygenated blood from the ductus with the mixed venous blood from the right ventricle. This finding is in agreement with the report of Eppinger, Burwell and Gross (5), which demonstrated that arterial blood is distributed throughout the pulmonary arterial system in patent ductus arteriosus.

The data presented thus far have described left to right extracardiac shunting of blood taking place via the ductus. However, the resting peripheral arterial O_2 saturation of 92 per cent and the post-exercise saturation of 88 per cent (Table III) suggest the simultaneous occurrence of right to left shunting of blood. It hardly seems likely that there could have been reciprocal shunting through the ductus in view of the existing pressure gradient between the aorta and pulmonary artery. The similarity in the O_2 content of right auricular and ventricular bloods did not indicate that intracardiac mixture of venous and arterial blood was taking place. To explain peripheral O_2 unsaturation

in this case there are the remaining possibilities of deficient oxygenation or arteriovenous shunting in the lung per se.

Following completion of the special tests, the patient was operated on. After the left pleural cavity had been entered, a thrill could be felt over the pulmonary artery. A large patent ductus was found. Pressure on the ductus abolished the thrill. The ductus was then ligated. At the end of the procedure the thrill was absent. The postoperating course was uneventful, and a final physical examination before discharge from the hospital uncovered no residual heart disease.

Case 4, M. B., was a seventeen year old female referred to the laboratory for study in January of 1947. As far as her parents knew, she was normal at birth. At the age of one year, during an attack of pneumonia, the presence of congenital heart disease was made known to the parents. Cyanosis of the lips and face, as well as clubbing of the fingers and toes, became apparent at the age of two years and had been slowly progressive ever since. When seven years old the child had a brief period of unconsciousness followed by weakness of the left foot, which gradually improved. In recent years there had been many spontaneous spells of weakness, shortness of breath, palpitation of the heart, and intensification of cyanosis. Exercise tolerance was severely limited but varied with weather conditions. Several venesections performed during 1946 were followed in 24 hours by definite improvement in all her complaints.

When examined she was a poorly nourished underdeveloped girl. There was marked cyanosis of the face, lips, and nail beds, as well as clubbing of fingers and toes. Her posture was poor because of a kyphoscoliosis involving the lower thoracic and upper lumbar spines. Positive findings were confined chiefly to the heart. The heart did not seem enlarged and a thrill was not present. The sounds were of good quality with the rhythm regular, but a loud high-pitched blowing systolic murmur was heard over the entire precordium. It was at a maximum in the second left intercostal space. A diastolic murmur was not audible. The blood pressure in the arms was 130/100 mm. Hg. The remainder of the examination was not unusual.

Under the fluoroscope the heart was not enlarged. The aorta descended on the left. The pulmonary conus was not full in any projection. However, the pulmonary artery was prominent in the anteroposterior view and plainly crossed the aortic window in the left anterior-oblique position. Pulsations were not seen in the lung fields.

Electrocardiographic tracings with the standard leads revealed a deviation of the electrical axis to the right, and right ventricular hypertrophy with the precordial leads. Routine laboratory examinations resulted in a red blood cell count of 10.1 millions, a hemoglobin of 21.5 grams (Sahli), a hematocrit of 77 per cent, a non-protein nitrogen of 53 mgms. per cent, and a peripheral arterial O_2 saturation of 72 per cent.

Because of the large pulmonary artery seen at fluoroscopy, it was not clear whether the cyanosis was part of the symptomatology of the tetralogy of Fallot or due to some other abnormality. For this reason the patient was referred to the laboratory for further study.

Results of physiological tests: Some of the significant data derived from the tests are portrayed in Figure 4. Pulmonary capillary flow was

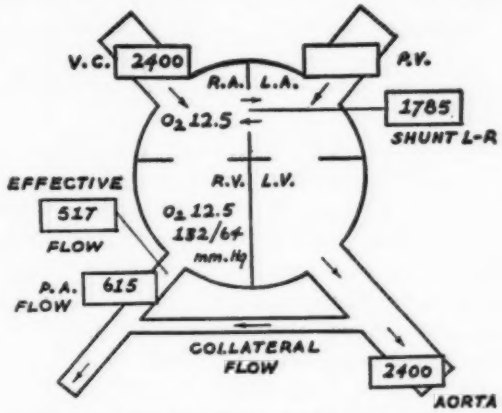

FIG. 4. illustrates the results from the physiological procedures in Case 4 (M. B.). Pulmonic stenosis is indicated by the volume of blood flow through the pulmonary artery which is 615 cc. Absence of a ventricular septal defect is suggested by the identical oxygen content of auricular and ventricular bloods. Presence of an auricular septal defect might have been revealed by the oxygen content of vena caval blood. The intracardiac shunt is predominantly right to left. Very little mixing occurs in the auricles because the effective pulmonary blood flow is only 100 cc. less than the pulmonary artery blood flow.

not measured in this individual. As a result the collateral blood flow to the lungs and aortic output could not be determined. The O_2 contents of right auricular and ventricular blood obtained by catheterization were identical (Table II). These observations were in contrast to the findings in Cases 1 and 2 where a significant O_2 gradient between the two chambers was encountered. Because of this finding, it was assumed that there was no interventricular septal defect. In the presence of an interventricular septal defect the O_2 content of blood from the ventricle would most likely have been higher than that of the

auricle (1, 2). An important omission during the heart catheterization was the failure to procure a blood sample from the vena cava which might have provided definite evidence for the presence of the persistent foramen ovale found at necropsy.

The O_2 content of pulmonary artery blood was 3 volumes per cent higher than that of the right ventricle (Table II). For the reasons oulined below, the O_2 content of right ventricular blood was employed in calculating pulmonary artery blood flow (Formula 2). The blood flow through the pulmonary artery was found to be 615 cc. This indication of a severe stenosis was in keeping with the conditions found at necropsy.

The systemic blood flow was 2400 cc. (Table II). There is the possibility that auricular blood was not truly representative of mixed venous blood and higher in O_2 content because of interauricular mixture of venous and oxygenated blood. For this reason the calculated systemic blood flow might have been greater than the true flow. Calculation of the effective pulmonary blood flow, which was 517 cc., suffered from the same criticism. As a sequel, the volume of the intracardiac shunt might have been less than the 1785 cc. derived (Table II).

Supporting the diagnosis of pulmonary stenosis were the results from the exercise test (Table III). The ratio, O_2 consumed per liter of ventilation, fell from a resting value of 20.9 to 16.0, and the CO_2 ratio also declined. There was also a fall in the peripheral blood O_2 saturation from a resting value of 51.2 per cent to 37.2 per cent. From the latter result it was inferred that venous blood with a lesser O_2 content or in greater quantities was shunted to the left side during exercise.

Comment: One of the criteria for location of the site of the intracardiac shunt is the relative O_2 content of the blood in the heart chambers. Auricular septal defects, as subsequent experience in this laboratory has shown, provide the same opportunity for mixing of venous and oxygenated blood as do ventricular septal defects. In dogs, Brannon, Weems and Warren (8) have also found the O_2 content of auricular blood significantly higher than that of the venae cavae in auricular septal defects. In the case under discussion it could not have been said that an interauricular shunt was present without a vena cava blood sample. In the absence of a shunt, peripheral O_2 unsaturation would have had to be explained on the basis of some interference with oxygen-

ation in the lungs. The conclusions drawn from such a line of reasoning would have been in conflict with evidence derived from the history, physical examination, and the sum total of the circulatory measurements.

During the catheterization the catheter tip was passed into the pulmonary artery, a surprising occurrence in view of the marked stenosis of the orifice of that vessel found at postmortem examination. The blood sample obtained from the pulmonary artery was nearly three volumes per cent higher in content of O_2 than that from the right ventricle. (Table II). In the absence of a patent ductus arteriosus there seemed to be two ways to explain this difference in O_2 content. One was that the catheter blood sample represented oxygenated blood drawn through the capillaries in retrograde fashion from the finer radicals of the pulmonary vein (9). The second was that oxygenated blood contributed by collaterals from systemic vessels to the pulmonary artery was sampled (10). In favor of the latter explanation was the fairly close correspondence between the pulmonary arterial blood O_2 content of 15.4 vols. per cent and that of the femoral artery with 16.4 vols. per cent (Table II). To have employed the O_2 content of pulmonary arterial blood to calculate pulmonary artery flow would have resulted in an exaggerated flow through that vessel.

The blood pressure in the right ventricle, recorded with the Hamilton manometer, was 132/64 mm. Hg (Fig. 4). The height of the systolic pressure, some 100 mm. above the normal (7), was in keeping with those found in pulmonary stenosis of the tetralogy of Fallot (1). In view of the postmortem findings, the value for systolic pressure obtained suggested that the elevation was a result solely of stenosis. In the tetralogy of Fallot and Eisenmenger's complex there are, in addition to pulmonic stenosis, the overriding aorta and the interventricular septal defect to explain the elevations in systolic pressures found (1, 2). The elevation of the diastolic pressure recorded in this case could not be explained logically.

Following performance of the special tests, operation was attempted on January 22, 1947. As the pectoral muscle was being incised, tachycardia was noticed by the anesthetist. Soon thereafter the pulse weakened, became unobtainable, and never recovered.

At postmortem examination, collateral vessels were found coursing

from intercostal arteries through pleural adhesions to the lungs. A branch of the right internal mammary artery passed anomalously to the right middle lobe of the lung. In the heart, the foramen ovale was widely patent. The right ventricular wall was hypertrophied. An area of stenosis was present at the pulmonary valve where the leaflets fused and projected into the pulmonary artery to form a conelike exit. The opening into the artery was 2 mm. in diameter. Beyond the valve the artery was normal in size with the left branch somewhat dilated. Several supernumerary bronchial arteries arose from the aorta. In summary, then, this was not the tetralogy of Fallot but pulmonary stenosis associated with a patent foramen ovale.

Case 5, W. G., was a sixteen year old boy referred to the laboratory for special studies in January of 1947. This patient was normal in appearance at birth and progressed satisfactorily until he was ready to enter school at five years of age. At that time, during a pre-school physical examination, a heart murmur was discovered. It was not until he was seven years old that blueness of the mucous membranes appeared. Simultaneously it was noticed that his tolerance for exercise was less than that of his playmates. In the space of a few years thereafter all of his symptoms, including cyanosis, dyspnea, and orthopnea, were intensified. His exercise tolerance soon became limited to walking a distance of several city blocks. At the age of twelve years he learned that squatting would relieve his shortness of breath. During the last two years he had appeared to lose ground rapidly. In the fall of 1946 a number of diagnostic tests, among them catheterization of the heart and angiocardiography, were performed at several other clinics with inconclusive results.

On physical examination performed in January of 1947 he was found to be a thin boy with intense diffuse cyanosis and marked clubbing of the fingers and toes. Percussion revealed the heart to be enlarged to the right and left. A diffuse systolic thrill was felt particularly well along the left sternal border. Heart sounds were of fair quality and the rhythm was regular. Over the entire precordium there was a loud rough systolic murmur heard maximally in the fourth left intercostal space. The murmur was transmitted toward the apex. The blood pressure in the arm was 96/70 mm. Hg. The remainder of the physical examination was not unusual.

Under the fluoroscope in the anteroposterior view the heart was enlarged to the left and right. There was a fulness in the region of the pulmonary conus. In the left antero-oblique position an unusual prominence, probably the upper portion of the right ventricle, was noted below the arch of the aorta. In the same view the left ventricle was much enlarged and the pulmonary window obliterated. Vascular markings were increased in the lung fields. Minimal expansile pulsations in the right hilar region were thought to be normal for an individual sixteen years old.

Electrocardiographic tracings with standard leads revealed right axis deviation and right ventricular hypertrophy with the chest leads. Routine laboratory examinations resulted in a red blood cell count of 8.8 millions, a hemoglobin of 23 grams (Sahli), a hematocrit of 74.5 per cent, a non-protein nitrogen of 48 mgms. per cent, and a peripheral arterial O_2 saturation of 78 per cent. The atypical history of this patient and the finding of a large pulmonary conus at fluoroscopy called for further investigation before operation could be countenanced.

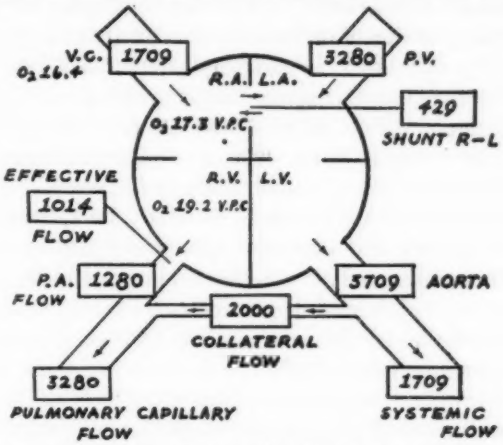

FIG. 5. illustrates the results from the physiological procedures in Case 5 (W G.). A large pulmonary conus was seen on fluoroscopy. However, pulmonic stenosis is indicated by the volume of blood flow through the pulmonary artery which is 1280 cc. The site of the intracardiac shunt is thought to be auricular because of the gradient in O_2 content between vena caval and auricular bloods (Table II). The presence of a ventricular septal defect is less likely since the oxygen content of some auricular blood samples exceeds that of ventricular blood (Table II). A large collateral circulation to the lungs demonstrated here as 2000 cc. was found at operation.

Results of physiological tests: Some of the significant data are presented in Figure 5. Pulmonary capillary blood flow (Table I) was 3280 cc., a volume slightly above the average normal cardiac index (4). When the heart was catheterized the catheter entered the right side into what appeared to be a large auricular cavity. The pressures in this chamber, 25/11 mm. Hg, showed an increase in systolic and diastolic levels over normal auricular pressures (1). A series of blood samples taken from various auricular locations ranged from 17.3 to 21.4 volumes

per cent in O_2 content (Table II). The O_2 contents of blood samples from this chamber were at least one volume per cent higher than those of the vena cava (Table II). The experience here was somewhat like that in Case 1 of this report where a single auricle was later found at postmortem examination.

The right ventricle was located with difficulty in a downward and posterior location. It was only by observing continuous optical pressures during manipulation of the catheter that an area of high pressure (132/21 mm. Hg) was found. Pulmonary artery blood flow employing right ventricular blood O_2 content was computed to be 1280 cc., less than half the normal cardiac index (Table II) (4). Collateral blood flow to the lungs (Formula 3) was 2000 cc., a volume in keeping with the great number of collateral vessels found at operation.

In calculating systemic and effective pulmonary flows, the difficulties experienced in Cases 1 and 4 in this paper were again encountered. Lacking a representative sample of mixed venous blood from the right auricle because of admixture of oxygenated blood in that chamber, the blood O_2 content of the superior vena cava was again employed for these calculations. Volume flows of 1700 cc. for systemic blood flow and 1010 for effective pulmonary flow were thus obtained (Table II). The overall intracardiac shunt, probably interauricular in location, was 429 cc. and directed from right to left (Table II).

Performance of the exercise test yielded results compatible with the circulatory measurements already described. Both ratios, CO_2 produced and O_2 consumed per liter of ventilation, fell during exercise (Table III). This was confirmation for the diagnosis of pulmonary stenosis.

Comment: Only two of the anatomical abnormalities predicted by the circulatory measurements could be confirmed in this case because of the limited opportunity for exploration at operation. A large collateral circulation, thought to be about 2000 cc. preoperatively, was found. Reduced pulmonary artery blood flow was confirmed by the finding of a small pulmonary artery in which the pressure was visibly decreased.

There seemed to be little doubt that intracardiac mixture of venous and arterial blood was taking place. Right to left shunting of blood was indicated by the peripheral arterial O_2 saturation of 78 per cent

(Table II). Probably there was left to right shunting as well because the effective blood flow to the lungs was less than the pulmonary artery flow. However, despite reciprocal mixing of blood, the predominant direction of the intracardiac shunt was from right to left. Once having established the presence of the shunt, a prerequisite for operation, its location was relatively unimportant from the standpoint of operative interference. Since the O_2 content of right auricular blood exceeded that of the superior vena cava, by at least one volume per cent, it seemed that the site of the shunt was auricular (Table II).

Location of the right ventricle in this case was accomplished by the discovery of an area of elevated pressure within the heart, rather than by fluoroscopic observation of the catheter movements. The blood O_2 content in this area indicated that the right ventricle rather than the left had been entered (Table II). Without this ventricular sample the pulmonary artery blood flow could not have been determined. The level of the systolic pressure in the right ventricle provided added confirmation for the diagnosis of pulmonary stenosis.

Following the performance of the tests described, operation was performed on February 1, 1947. It was evident, once the pleura was opened, that there were a great many collateral vessels in the mediastinum. An extremely small pulmonary artery was ultimately dissected out and pulsations in it were absent. Because of the small size of the artery an end-to-end anastomosis between right subclavian and main right pulmonary arteries was effected. When the anastomosis was completed a thrill could be felt and the pulmonary artery ballooned out as a large vessel.

SUMMARY

From a series of patients with congenital heart disease studied in this laboratory there were selected for presentation the histories of five individuals who required the application of physiological tests before surgery could be attempted. The cases were chosen because they illustrate some of the diagnostic problems amenable to solution by the procedures described. Operative or postmortem findings were available to validate allegations made on the basis of the tests performed.

In the first case, the diagnosis of pulmonary stenosis was not apparent from the physical examination and the fluoroscopic findings

were atypical. Catheterization of the right ventricle and pulmonary vein revealed a reduction in pulmonary artery blood flow. A decreased effective blood flow to the lungs was found by calculation. These findings, plus the diagnosis of an intracardiac shunt, indicated that the creation of an artificial ductus might be helpful (11). Catheterization of the heart revealed abnormal entry of a vena cava, an interauricular communication, and a virtual single ventricle.

The diagnosis of tetralogy of Fallot was confirmed by physiological studies in the second case. A large collateral circulation to the lungs predicted by the tests was found at operation. The possible relation of the large collateral circulation to the postoperative course of this patient was discussed.

In the third case, with classical signs of a persistent ductus arteriosus, certain elements of the history were unusual. By determination of pulmonary capillary blood flow and calculation of pulmonary artery blood flow, the volume flow through the ductus was found to be 1150 cc. At operation a large patent ductus was ligated.

In the fourth case, a large pulmonary artery seen at fluoroscopy created doubt as to the presence of pulmonic stenosis. Catheterization of the heart and performance of a standard exercise test revealed a reduction in pulmonary artery blood flow, a reduction in effective blood flow to the lungs, and the probable presence of an intracardiac shunt. Pulmonary stenosis was also indicated by an elevated right intraventricular pressure and a reduction in pulmonary artery pressure. These findings were sufficient to warrant operation. A patent foramen ovale and stenosis of the pulmonary valve were later found within the heart.

A prominent pulmonary conus, increased lung markings, and pulsations in the lung fields were all found at fluoroscopy in the fifth case. These findings seemed to contraindicate the presence of pulmonic stenosis. Performance of the exercise test and catheterization of the right ventricle indicated that there was pulmonary stenosis and reduced effective blood flow to the lungs. A large collateral circulation to the lungs, calculated from the physiological data, was found at operation. Reduced pulmonary artery blood flow was confirmed by the finding of a small pulmonary artery in which pulsations were absent.

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BIBLIOGRAPHY

1. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr., Physiological studies in congenital heart disease. II. Results of preoperative studies in patients with tetralogy of Fallot, Bull. Johns Hopkins Hosp. **80:** 121, 1947.
2. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr., Physiological studies in congenital heart disease. III. Results in five cases of Eisenmenger's complex, Bull. Johns Hopkins Hosp. **80:** 323, 1947.
3. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr., Physiological studies in congenital heart disease. I. Procedures, Bull. Johns Hopkins Hosp. **80:** 107, 1947.
4. Cournand, A., Measurement of cardiac output in man using right heart catheterization; Description of technique; Discussion of validity and of place in study of circulation, Federation Proc. **4:** 207, 1945.
5. Eppinger, E. C., Burwell, C. S., and Gross, R. E., Effects of patent ductus arteriosus on circulation. J. Clin. Investigation **20:** 127, 1941.
6. Warren, J. V., Stead, E. A., and Brannon, E. S., The cardiac output in man: A study of some of the errors in the method of right heart catheterization, Am. J. Physiol. **145:** No. 4, 458, 1946.
7. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr., Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardiovascular disease, J. Clin. Investigation **25:** 639, 1946.
8. Brannon, E. S., Weens, H. S., and Warren, J. V., Atrial septal defect; Study of hemodynamics by technique of right heart catheterization, Am. J. Med. Sci. **210:** 480, 1945.
9. Dexter, L., Personal communication.
10. Duncan, G. W., Personal communication.
11. Blalock, A., and Taussig, H. B., Surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia, J.A.M.A **128:** 189, 1945.